<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>New data from PrEP study shed light on adherence, bone mineral loss and resistance</td>
</tr>
<tr>
<td>2.</td>
<td>Does immune reconstitution contribute to ART-related bone loss?</td>
</tr>
<tr>
<td>3.</td>
<td>First pills-versus-gel trial finds US women prefer oral PrEP</td>
</tr>
<tr>
<td>4.</td>
<td>Previous Syphilis Infection Might Cause Poorer Brain Function for People With HIV</td>
</tr>
<tr>
<td>5.</td>
<td>Recombinant Interleukin-7 (CYT107) Expands CD4 T-Cells In Gut Mucosa Of Chronically HIV Infected Immunological Non-Responder Patients</td>
</tr>
<tr>
<td>6.</td>
<td>Other Routes to HIV Drug Assistance</td>
</tr>
<tr>
<td>7.</td>
<td>When HIV Moves Into Nursing Homes</td>
</tr>
<tr>
<td>8.</td>
<td>Babies Who Escape HIV Face Other Death Risks: Study</td>
</tr>
<tr>
<td>9.</td>
<td>New drug regimens cut HIV spread from mother to infant</td>
</tr>
<tr>
<td>10.</td>
<td>Research shows how bacteria communicate with each other</td>
</tr>
<tr>
<td>11.</td>
<td>Amyotrophic Lateral Sclerosis (ALS) Could Be Caused by a Retrovirus, Study Suggests</td>
</tr>
<tr>
<td>12.</td>
<td>HIV Vaccine Impacts the Genetic Makeup of the Virus</td>
</tr>
<tr>
<td>13.</td>
<td>Is HIV drug resistance spreading? Early warning signals say 'yes'</td>
</tr>
<tr>
<td>14.</td>
<td>Forecasters agree PrEP/microbicides could cut HIV infections in South Africa</td>
</tr>
<tr>
<td>15.</td>
<td>Partners study expands our knowledge of HIV transmission risk</td>
</tr>
<tr>
<td>16.</td>
<td>More US Youth Say They Are Not Having Sex</td>
</tr>
<tr>
<td>17.</td>
<td>Female Condoms Are Gaining Ground</td>
</tr>
<tr>
<td>18.</td>
<td>Church Leader Reverses Stance on HIV, Reaches Out to Those Affected</td>
</tr>
<tr>
<td>19.</td>
<td>CROI: Five-Drug HIV Therapy No Better than Standard</td>
</tr>
<tr>
<td>20.</td>
<td>No More Science Fiction—HIV Gene Therapy Delivers</td>
</tr>
<tr>
<td>21.</td>
<td>New microscope produces dazzling 3-D movies of live cells</td>
</tr>
<tr>
<td>22.</td>
<td>Vaccinated children not at higher risk of infections or allergic diseases</td>
</tr>
<tr>
<td>23.</td>
<td>6 months of nevirapine prophylaxis for breastfeeding infants reduces transmission by 76% if mother not on ART</td>
</tr>
<tr>
<td>24.</td>
<td>No Quiet Old Age for South Africa's Grannies</td>
</tr>
<tr>
<td>25.</td>
<td>Helicobacter Pylori Infection Linked to Decreased Iron Levels in Otherwise Healthy Children</td>
</tr>
<tr>
<td>26.</td>
<td>Life-Saving Blood Test for Fungal Meningitis, a Leading Cause of AIDS-Related Deaths in Developing Countries</td>
</tr>
<tr>
<td>27.</td>
<td>Roundworm could provide new treatment for sepsis</td>
</tr>
<tr>
<td>28.</td>
<td>Cancer in HIV-positive patients</td>
</tr>
<tr>
<td>29.</td>
<td>Experts Develop Tool to Predict Course of Haiti's Cholera Outbreak, Offer Disease Control Strategies for Immediate Implementation</td>
</tr>
<tr>
<td>30.</td>
<td>Class of Potent Anti-Cancer Compounds Discovered</td>
</tr>
<tr>
<td>31.</td>
<td>New Compound Rids Cells of Alzheimer Protein Debris</td>
</tr>
<tr>
<td>32.</td>
<td>Rwanda Looks to Vasectomy to Tackle Population Growth</td>
</tr>
<tr>
<td>33.</td>
<td>Malaria’s Weakest Link: Class of Chemotherapy Drugs Also Kills the Parasite That Causes Malaria</td>
</tr>
<tr>
<td>34.</td>
<td>At least one in six patients maintains a viral load over one hundred thousand</td>
</tr>
<tr>
<td>35.</td>
<td>Russia discriminates against man with HIV—court</td>
</tr>
<tr>
<td>36.</td>
<td>Taiwan scientists document first case of knife-wound HIV infection</td>
</tr>
<tr>
<td>37.</td>
<td>Record Numbers of New Zealand Gay, Bisexual Men Diagnosed with HIV</td>
</tr>
<tr>
<td>38.</td>
<td>Help on Horseback for AIDS Sufferers in Mountain Kingdom</td>
</tr>
<tr>
<td>39.</td>
<td>Antiretroviral Therapy and Sexual Behavior in Uganda: A Cohort Study</td>
</tr>
<tr>
<td>40.</td>
<td>Research suggests HIV-infected patients at higher risk for bone fractures</td>
</tr>
<tr>
<td>41.</td>
<td>Missing DNA Helps Make Us Human</td>
</tr>
<tr>
<td>42.</td>
<td>Function of 'Junk DNA' in Human Genes</td>
</tr>
<tr>
<td>43.</td>
<td>Gaddafi's HIV Shakedown</td>
</tr>
<tr>
<td>44.</td>
<td>Gilead's High Bar for AIDS Drugs Means New Development Withers</td>
</tr>
<tr>
<td>45.</td>
<td>An inside look at how the elite control HIV</td>
</tr>
<tr>
<td>46.</td>
<td>Study helps explain how pathogenic E. coli bacterium causes illness</td>
</tr>
<tr>
<td>47.</td>
<td>Early success of anti-HIV preventive oral drug regimen is promising, but questions remain</td>
</tr>
<tr>
<td>48.</td>
<td>Pushing HIV out the Door: How Host Factors Aid in the Release of HIV Particles</td>
</tr>
<tr>
<td>49.</td>
<td>Infographic: Epigenetics—A Primer</td>
</tr>
<tr>
<td>50.</td>
<td>Epigenetic Changes in Cancer</td>
</tr>
<tr>
<td>51.</td>
<td>Missing reference on DNA methylation of tumors</td>
</tr>
<tr>
<td>52.</td>
<td>Epigenetics and Society</td>
</tr>
<tr>
<td>53.</td>
<td>The Mark of Faith</td>
</tr>
<tr>
<td>54.</td>
<td>The Evolution of Credibility</td>
</tr>
</tbody>
</table>
55. Come Inside
56. Environmental Impact (long)
57. An HIV Strategy Invites Addicts In
58. Increased Rates of Bone Fracture Among HIV-Infected Persons in the HIV Outpatient Study (HOPS) Compared with the US General Population, 2000-2006
59. Study shows importance of resistance testing before start of HIV treatment
60. iTherX Initiates Phase 1b Study of First-in-Class Hepatitis C Virus Entry Inhibitor ITX-5061—Preclinical Studies Show that ITX-5061 Prevents Hepatitis C from Invading Liver Cells
61. New Vaccine Candidate Shows Strong Potential To Prevent Highly Contagious Norovirus
62. HPV Linked to More Cancers; Prevention Strategy Could Include Male Vaccine, Says Oncologist
63. Spatial Clustering of HIV Prevalence in Atlanta, Georgia, and Population Characteristics Associated with Case Concentrations
64. Hampton Roads Has Some of the Highest STD Rates in the Nation
65. Guatemalans Sue over 1940s US Syphilis Experiments
66. AIDS Drugs Slow Deaths in South Africa: Study
67. Normally tranquil Botswana has plunged into a fierce public debate about whether homosexuality is "un-African", sparked by a new lawsuit against the country's sodomy law
68. Rubaramira wants HIV/AIDS Bill shelved Tuesday, 15th March, 2011
69. US: State public health officials condemn 'stigmatising, harmful' HIV-specific laws
70. National Hiv/Aids Strategy Imperative: Fighting Stigma And Discrimination By Repealing HIV-Specific Criminal Statutes
71. Cholera Epidemic In Haiti Could Affect Twice As Many As Previously Estimated
72. Artesunate More Effective Than Quinine At Preventing Malaria Deaths, Review Shows
73. Cash Incentives Have Potential To Prevent HIV Among Young Sub-Saharan African Women
74. Breaking the mucus barrier unveils cancer cell secrets
75. In New York, A Rare Case of HIV Transmission From a Live Organ Donor
76. Rwanda: UNAIDS Chief Commends New Circumcision Device
77. Female condoms are gaining ground
78. Cholera Vaccines Can Prevent Up To 60% Of Cases In First Two Years Following Vaccination
79. Why Are the Elderly So Vulnerable to Pneumonia?
80. Developing a Universal Flu Vaccine?
81. Improving the Infant Gut 'microbiome'
82. Comparison of Wiping Away Bacteria With Disinfectant Wipes or a Tissue Moistened With Saline
83. Saint Patrick Didn't Have It Easy ... but at Least the Food Wasn't Bad
84. Transmissible treatment proposed for HIV could target superspreaders to curb epidemic
85. Transplant Patient Got AIDS from New Kidney
86. Nevirapine for breastfeeding infants: benefit of 6-week course still evident after one year
87. Gut bugs to lungs' rescue
88. Bitter Pill
89. The Birds and the Bees
90. MMWR Reports on Premastication of Food by Caregivers of HIV-Exposed Children
91. Poor lower-limb strength common in patients with long-term HIV infection, French study finds
92. Rural girls cheated into marrying HIV carriers
93. Senate Adjusts Religious Aspect of Vaccine Bill
94. Board Says Doctor Admitted He Reused Biopsy Needle Guides
95. South Africans with AIDS Fear New Drug Crimes
96. Studies Shed Further Light on Cardiovascular Disease among People with HIV
97. Experts Warn Of Global Water Shortages Ahead Of World Water Day
98. Scientists Refine Efforts To Develop Semi-Synthetic Artemisinin
99. Mutant Prions Help Cells Foil Harmful Protein Misfolding
100. Gut Bacteria Can Control Organ Functions
102. High prevalence and incidence of anal pre-cancerous lesions in men with HIV; HAART has little impact
103. Justice Department Issues Letter Regarding Illegal Exclusion of Individuals with HIV/AIDS from Occupational Training and State Licensing
104. Sex Education Bill Signed
105. Drug Resistance Hampers Fight Against Tuberculosis
106. Social Messages, Social Context, and Sexual Health: Voices of Urban African-American Youth
107. Speakers at Forum Debate Condoms in City Schools
Evolution Project for Black Gay Men Opens New Facility
Quinn's University puts over 2,400 food scares under the microscope
Newly discovered virus implicated in deadly Chinese outbreaks
How Different Strains of Parasite Infection Affect Behavior Differently
Fewer Bats Carry Rabies Than Thought
A Better Test for Human Papillomavirus
AIDS Tests Come to South Africa's Schools
Could a Transmissible Treatment Help Curb HIV Epidemic?
Chikungunya: The Key Role of 'Innate Immunity'
The Killer Within: A Novel Bacterial Suicide Mechanism
National Organization Adds Voice Against HIV-Specific Criminal Laws
Taylor Was Early and Tireless AIDS/HIV Advocate
Sexual Risk Behaviors Among Teens at an Urban Emergency Department: Relationship with Violent Behaviors and Substance Use
Glimpse of How the 'Code' of Life May Have Emerged
'Knowing It In Your Gut': Cross-Talk Between Human Gut Bacteria and Brain
Epigenomic Findings Illuminate Veiled Variants: Study Assigns Meaning to Regions Beyond Genes With Implications for Studies of Common Diseases
Gay men reduce their risk behaviour after HIV diagnosis, studies find, but disagree on how much by Fertility treatment can use semen from men with HIV
Glaxo Accuses Abbott of Stifling Competition on AIDS Drug
Improving Adherence and Clinical Outcomes Through an HIV Pharmacist's Interventions
Do Black Patients Respond Less Well to Antiretroviral Therapy?
Cruise Ship Norovirus Outbreak Highlights How Infections Spread
MRSA Infection Shown to Be Seasonal
Study Reports High Rate of Selection for Lamivudine Mutations in HIV-Infected, Treatment-Naive Children at the Time of Virologic Failure
Mitotic Hijacker
European guidance published on the use of tropism tests in routine HIV care
Dark side of giving: The rise of philanthro-capitalism (long)
Reports say Ugandan anti-gay bill has been killed
Manila interfaith rally draws 40,000 faithful vs. RH bill
Sexually liberated, or just badly brought up? (long)
Two-Thirds of South African Women at Risk for Cervical Cancer
Integrated Behavioral Intervention to Improve HIV/AIDS Treatment Adherence and Reduce HIV Transmission
Research proves no 2 of us are alike, even identical twins
'Near perfect' adherence in early stages of Partners PrEP study
Watch for malnutrition risk in children with HIV after starting ART
Charge of infecting partner with HIV quashed
Could HIV-infected organs save lives?
Rwanda Investigating Adult Male Circumcision Without Anesthesia
Public Campaign Ad Featuring Patient Draws Criticism
Association of Aging and Survival in a Large HIV-Infected Cohort on Antiretroviral Therapy
Volunteers Needed for HIV Trials
Vaccine Used in STEP Trial Alters HIV Genes
HIV Enters and Injures Brain Early
Breastfeeding infants with HIV may develop drug resistance from ARVs in breast milk
U.S. jury rejects Glaxo antitrust claims vs Abbott
U.N. Secretary-General Releases Report Assessing Global Response To HIV/AIDS
A new signaling pathway of the immune system is elucidated
Scientists discover new drug target for inflammatory bowel disease: cytokine (IL-23)
Intelligent design: Engineered protein fragment blocks the AIDS virus from entering cells
Researchers need to engage lesbian, gay, bisexual, and transgender populations in health studies
Evolution: Not Only the Fittest Survive
New data from PrEP study shed light on adherence, bone mineral loss and resistance
Gus Cairns
Published: 02 March 2011

Near-perfect adherence to oral pre-exposure prophylaxis – taking HIV drugs to prevent HIV – may be achievable in the right settings, the eighteenth Conference on Retroviruses and Opportunistic Infections heard yesterday.

Participants from the US sites of the international iPrEx study of tenofovir/FTC (Truvada) pre-exposure prophylaxis (PrEP) in men who have sex with men and transsexual women had near-perfect adherence, compared with 50% adherence from other sites, new data presented at the conference shows.

Analysis also found that adherence in men who had the highest risk of acquiring HIV, by having unprotected receptive anal sex, was, at 76%, far higher than those at lower risk, so participants were tempering their pill-taking to their perceived risk.

Another substudy has found that taking Truvada resulted in a small but significant loss in bone mineral density in participants. But it also found that participants’ bone mineral density at the start of the study was considerably lower than would have been expected in men their age.

Resistance tests uncovered no drug resistance in men who seroconverted (became infected with HIV) on the trial, but did find that one participant who took placebo had a small amount of virus with the K65R resistance mutation to tenofovir.

At a discussion forum on iPrEx and on the CAPRISA 004 microbicide trial, lead investigator Bob Grant announced that the US Food and Drug Administration had agreed that the iPrEx trial findings were sufficient for the FDA to move ahead and consider changing the indication for Truvada to include using it to prevent HIV.

PrEP, as a result, might be approved in the US by the end of this year.

Updated trial results
In the paper published on the trial findings in the New England Journal of Medicine last November, data were given up to May 2010. Bob Grant presented final figures for the trial, whose last participants left the trial in August 2010.

The final tally was that 130 HIV infections were seen in the 2499 men taking part in the trial, 48 of those taking Truvada and 82 on placebo, a rate of 2.6% a year. There were also 10 infections in men who had acute HIV symptoms at the time they enrolled, two of whom appear to have acquired resistance to FTC, and six infections in the three months immediately following the trial, four of them in men who had taken Truvada.

This means that the final efficacy figure in the ‘modified intent to treat’ (MITT) analysis, which excluded the men who had HIV at the start of the study and ignores factors like adherence and sexual risk, was 42%.

Efficacy was greater in men over 25 (56%), in men who reported greater than 90% adherence (68%), and, for reasons that are unclear, in the relatively small number of men who were circumcised (76%).

Adherence
One of the surprises of the original trial was that while mean reported adherence was 95%, a study of drug levels found that only 50% of a random sample of men who did not acquire HIV had detectable drug in their white blood cells. Only 9% of those who seroconverted had any drug in their cells either. Drug can be detected in cells for several weeks and this shows, in the words of Bob Grant, that “people were either taking it daily or not at all”.

A new analysis of drug levels in 179 participants by Peter Anderson of the University of Colorado confirmed that only 50% had detectable tenofovir in their cells and 62% detectable FTC. However 97% of the 227 participants from the two sites in the USA, in San Francisco and Boston, had detectable drug, showing that adherence was near-perfect in this more treatment-literate group. It also confirmed that adherence was better in men over 25 (73%) than men under 25 (44%).

Adherence analysis also showed that participants tempered their adherence according to their level of risk; 76% of those who had had unprotected receptive anal sex in the previous twelve weeks had significant drug levels versus 36% of those who had not and 25% of those who had had no sex at all.

Rivet Amico of the University of Connecticut presented an analysis of how self-reporting and pill counts correlated with actual adherence in the study. There were four measures of adherence taken during the study: self-reports by interview and by computer-assisted interview, pill count of the number of pills dispensed minus those returned, and the medication possession ratio (MPR), which was a measure, based
on refill rates, of how many pills the participants had relative to the number that would last exactly till the next visit (thus an MPR of 1.25 meant they had 25% more pills than the minimum needed).

MPR was the most accurate guide to actual adherence. Only 68% of those claiming 100% adherence by self-report were actually adherent; only 62% of those claiming 100% adherence by computer-assisted interview; and only 59% of those assessed as having 100% adherence by pill count. But 75% of those assessed as having 100% adherence by MPR actually were so. The overall ‘positive predictive value’ of a claim of 100% adherence was 69%, meaning that 31% of those assessed as having 100% adherence did not. The ‘negative predictive value’ of a claim of less than 100% adherence was 95%, however, meaning that self-reports of poor adherence could be relied on.

**Bone mineral density**

One concern in trials using tenofovir as post-exposure prophylaxis has been that all antiretrovirals seem to cause a transient loss in bone mineral density, but that this seems to be larger and in some studies persistent in people taking tenofovir.

A study of 2045 iPrEx participants using DEXA scans (Mulligan) found that bone mineral density (BMD) scores at trial recruitment were already lower than would have been expected in men of the same age. Twelve per cent of participants had a ‘Z score’ for BMD in their spine of more than minus two, meaning that they fell into the lowest 5% of BMD values for an average population. BMD scores in the hip were also lower than expected.

During the trial BMD declined approximately 0.6% further in the spine (though not in the hip) in people taking Truvada but did not decline in subjects taking placebo, during the first six months. In the minority of subjects so far measured out to 18 months it declined by 1%. Nine per cent of subjects on Truvada had a loss of more than 5% in their spinal BMD compared with 4% on placebo.

This 1% average decline compares with an average 2 to 4% decline in patients taking tenofovir for treatment. There appeared to be no clinical effects, but at present we only have data on most subjects for the first six months, so it is not known if this bone loss is progressive or will stabilise.

Another study of BMD was presented from a different PrEP study: the safety trial of tenofovir PrEP in 400 US gay men which ended in July 2010 (Liu). This substudy only looked at the 200 participants from San Francisco. It found a loss of about 2% BMD in the neck of the hip bone over two years, though not in the spine.

This study also found lower-than-expected BMD in study entrants. It found that men using amphetamines were six times more likely to report low BMD at baseline and users of poppers 4.5 times as likely; conversely men who took vitamin D, calcium or multivitamins were 70% less likely to report low BMD.

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**Does immune reconstitution contribute to ART-related bone loss?**

Liz Highleyman

Published: 02 March 2011

Immune recovery and T-cell restoration may play a key role in bone loss that occurs very soon after starting antiretroviral therapy, according to a small study presented on Tuesday at the 18th Conference on Retroviruses and Opportunistic Infections (CROI), taking place this week in Boston.

A growing body of evidence shows that bone loss commonly occurs after starting HIV treatment. This has been linked to specific drugs, in particular tenofovir (Viread), but also appears to be an effect of antiretroviral therapy (ART) more generally. Most research has looked at bone loss over time, however, and there are few data about changes immediately after starting therapy.

Ighovwerha Ofotokun, from Emory University in Atlanta, and colleagues, performed human and animal studies to evaluate when ART-related bone loss occurs and what might be its underlying cause.

In many diseases inflammation and T-cell activation contribute to bone loss by altering production of cytokines, or chemical messengers that affect bone build-up and breakdown. A cytokine known as RANKL...
stimulates osteoclasts, the cells that break down bone and promote resorption (loss and reassimilation) of its minerals, whilst a protein called osteoprotegerin binds to RANKL and protects against bone loss.

As considerable CD4 T-cell recovery occurs during the first 12 weeks on ART, the researchers looked at bone changes during this period. Most prior studies, in contrast, have looked at bone loss after six months or more.

Their first analysis included 20 HIV-positive individuals with an average age of 40 who started antiretroviral drugs for the first time. The mean CD4 count at the beginning of treatment was quite low, at 123 cells/mm$^3$.

Participants responded well to therapy, with all but one achieving undetectable viral load by week 24. At baseline and at weeks 2, 12 and 24, the researchers measured blood biomarkers of bone formation and resorption, namely RANKL, tumour necrosis factor alpha, osteocalcin (a protein produced by bone-building cells called osteoblasts) and CTx (a by-product of collagen breakdown).

The researchers noted a dramatic and unexpected early surge in bone resorption immediately after ART initiation. The large increase in bone loss markers was similar to changes seen in women at the menopause, Ofotokun said.

Bone loss was clearly evident by week 2 and peaked at week 12, but resorption markers remained significantly elevated at week 24. Of note, however: there was also a compensatory increase in markers of bone formation, explaining the absence of extreme bone loss.

To further explore the link between bone loss and immune reconstitution, the investigators then looked at an animal model of HIV disease reversal, using T-cell deficient mice that were given purified CD3 T-cells by adoptive transfer.

Here, too, they saw a surge in bone resorption, with CTx levels rising by more than 100%. By week 12 the mice showed reduced bone mineral density in the femur (thigh bone), tibia (shin bone) and lumbar spine. Unlike the humans, however, bone formation decreased in concert with increased resorption.

The researchers concluded that ART-related bone loss begins earlier than previously suspected after treatment initiation, driven at least in part by T-cell activation and reconstitution.

Although the data are not yet fully analysed, Ofotokun noted that there appears to be a correlation between the degree of bone resorption and magnitude of CD4 cell gains.

Some study participants took tenofovir, and the researchers are currently assessing the role of antiretroviral drug choice in early bone loss.

Knowing that bone resorption occurs so soon after starting treatment, Ofotokun suggested, may offer a window for pre-emptive interventions to prevent bone loss at the time of ART initiation.

**Reference**


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**First pills- versus- gel trial finds US women prefer oral PrEP**

Gus Cairns

Published: 02 March 2011

The first head-to-head trial directly comparing the acceptability of tenofovir pills and tenofovir microbicide gel to HIV-negative women has found that, while African women liked both products equally, three-quarters of US women preferred a pill.

The study also found, not unexpectedly, that concentrations of tenofovir in cells in the cervix and vagina were, respectively, 20 and 100 times higher in women using the gel than taking the pill. Although there is no definitive evidence yet, this suggests that a topical microbicide might be more fully protective against sexual infection than oral PrEP.

Conversely, concentrations of tenofovir in cells in the blood were 54 times higher in women taking oral PrEP than in those using a microbicide. The level reached in blood and blood cells in women using the microbicide gel was less than one-tenth of the minimum observed concentration of tenofovir required to inhibit HIV replication by 50% (the IC$_{50}$), and much lower than the average IC$_{50}$, indicating that levels of drug in the blood of microbicide users who become infected with HIV despite microbicide use are unlikely to generate resistance – thought this is also yet to be shown.

In the MTN-001 study, 144 women at seven sites in Africa and the US were randomised to take a daily tenofovir pill, use daily 1% tenofovir microbicide gel, or use both together. All women used all three regimens at some point during the study: women were randomised to use one regimen for six weeks, take a week’s break, then use another, and so on until they had used all three.
Self-reported adherence was 94% and did not differ between regimens but, as had been found in other prevention trials, actual adherence as measured by drug concentrations was in the range of 35% to 65%. There was a higher rate of nausea in women taking oral tenofovir (15% with solo tenofovir, 14% with both formulations) than in women using the gel alone (3%).

There was a rough symmetry in concentrations in genitals and blood according to whether women were taking the gel or the pill.

For instance, the concentration of tenofovir in the blood of women taking the pill was 332 nanograms per millilitre (ng/ml) but in the vagina only 0.2 ng/ml; conversely the concentration in the blood of women using the gel was 3.7 ng/ml but in vaginal tissues, 113 ng/ml. Tenofovir’s IC₅₀ (the concentration of drug needed to inhibit half the virus) is 220-500 ng/ml (Skowron and Ogden), but the drug, when administered as a microbicide, reached much higher concentrations in cells, which is where it need to do its work. However presenter Craig Hendrix did warn that “what is ‘enough’ for prevention is yet to be defined”.

Ninety-three per cent of women said they would use the tablet if they needed to in the future, 83% per cent the gel and 82% both formulations. This difference was driven entirely by women in the four US sites.

Seventy-three per cent of US women said they preferred to take an oral tenofovir pill, whereas African women preferred pill and gel about equally, with 42-44% each saying their first preference was the pill or the gel. Preference for gel in African women was driven by a number of African women who said they preferred the gel because it made sex better.

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Previous Syphilis Infection Might Cause Poorer Brain Function for People With HIV
March 1, 2011
By David Evans
HIV-positive people who have been infected with syphilis (Treponema pallidum) in the past might have poorer brain function than HIV-positive people who have never had it. These data were presented Monday, February 28, at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

In the past several years the dramatic early successes of combination antiretroviral (ARV) treatment for HIV—with dramatic drops in death rates and AIDS-related infection—have given way to a growing recognition that significant health complications remain even in the face of near–perfect viral control. One type of health problem that has captured researchers’ interests is damage to the network of cells that make up the brain and nervous system.

Data from a stack of research studies have confirmed that the pool of HIV in the brain is different from the HIV circulating in blood. While this is not entirely surprising—the brain is well protected from the rest of the body, and immune cells there differ somewhat from immune cells elsewhere—the implications of differing patterns of HIV reproduction are now being documented. These have included high rates of neurological damage in people with HIV. The damage in most people is so mild that it goes unrecognized, but researchers are worried that it could ultimately lead to higher rates of dementia as people get older.

Another infectious organism that can attack the brain is syphilis. In its later stages, syphilis in the brain (called neurosyphilis) can lead to a number of disconcerting symptoms, including problems with concentration, coordination and emotional disturbances. In people not infected with HIV, the course of untreated syphilis is typically quite slow; in fact, people must usually be infected for several years before neurosyphilis develops. In people with HIV, however, the disease course is more rapid, and untreated syphilis can begin affecting the brain within a matter of months.

Given the high rates of syphilis infection among people with HIV, Christina Marra, MD, from the University of Washington in Seattle grew concerned that the long-term impact of syphilis infection—even years after it was successfully treated—hadn’t been well documented in people with HIV.

To explore this further, she and her colleagues examined people enrolled in a larger study of HIV, ARVs and neurocognitive function called the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study. Out of a total of 1,574 people enrolled in CHARTER, Marra’s team found 82 people
who had positive rapid plasma reagin (RPR) test of their rectums, indicating that they had a history of syphilis. These people were matched to 52 similar HIV-positive people who had no history of syphilis infection.

Roughly three quarters of the participants were male, just over half were black, and 65 percent were taking ARV therapy. The average age of the participants was 41, and most had completed high school. Thirty-one of the 84 participants with a history of syphilis were found to have recent, untreated infection.

Marra and her colleagues found that a history of syphilis, both recent and past, resulted in lower neuropsychological performance based on two types of test. This was true even when they ruled out differences in reading skill and education. There was no difference in neuropsychological function between people recently infected (and untreated) and those who had syphilis in the past and who had been successfully treated.

The authors caution that further studies following people over time are needed to confirm these results and to determine the long-term impact, but they state that the results indicate that good syphilis screening programs are a necessity in HIV care and that people with a history of syphilis may need to have their cognitive function monitored more closely over time.

Recombinant Interleukin-7 (CYT107) Expands CD4 T-Cells In Gut Mucosa Of Chronically HIV Infected Immunological Non-Responder Patients

02 Mar 2011

Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, announced results of a multi-center Phase IIA study designed to investigate the potential of Interleukin-7 (CYT107) therapy to reconstitute CD4 T-cells in chronically HIV-1 infected patients whose CD4 T-cell counts remained low despite treatment with anti-retroviral-therapies (HAART). In addition to providing further evidence of the ability of IL-7 to stimulate the expansion of CD4 and CD8 T-cells in peripheral blood, the results demonstrate the importance of IL-7 in stimulating T-cell repopulation of the lymphoid tissue layer in the mucous membrane of the GI tract. This effect, previously demonstrated in SIV infected monkeys, is now confirmed by analysis of rectosigmoid biopsies in this study of HIV infected patients defined as Immunological Non-Responders (INR). The analysis of these mucosal gut biopsies shows a 3.93-fold increase in CD4 T-cell counts following IL-7 treatment. The data were presented at the 2011 Conference on Retroviruses and Opportunistic Infections (CROI) held in Boston, February 27-March 2.

The results of the Phase IIA study (Abstract #H-113: Recombinant Interleukin-7 (CYT107) Expands CD4 T-cells in Peripheral Blood and Gut Mucosa of Chronically HIV-Infected Immunological Non-Responder Patients, Irini Sereti, Jean-Pierre Routy, Margaret Fischl, Thérèse Croughs, Stéphanie Beq, Michel Morre, M R Boullassel, Michael Yao, William Thompson, and Michael M. Lederman) were presented by Irini Sereti, M.D., M.H.S., NIAID/NIH Study Investigator and INSPIRE 2 Study Co-Chair.

"CD4 T-cell depletion in gut mucosa is an early and key pathogenic event in HIV infection that is associated with T-cell activation [1] [2]," said Michel Morre, DVM, president and CEO of Cytheris.

"Despite successful anti-retroviral therapy (HAART), significant morbidity and mortality persists in HIV infection, particularly in patients who fail to restore normal CD4 T-cell counts. The results of the current study suggest that IL-7, which targets expansion of the T-cell pool in both peripheral blood and mucosal sites, may be able to play a pivotal role in immune restoration in chronic HIV infection."

Results of the Phase IIA (INSPIRE 2) Study

INSPIRE 2 is an open-label, multicenter Phase IIA study of CYT107 (IL-7) in chronically HIV-infected persons with CD4 T-cell counts between 101-400 cells/mm3 and plasma HIV RNA <50 copies/mL. Twelve patients were enrolled and received 20 mcg/kg/week of CYT107 for 3 weeks. All were evaluated at the planned primary end point at week 12 (CD4 expansion).

The 12 enrolled patients received three weekly injections of CYT107 that were clinically well tolerated and without serious adverse events. Seven patients had transient increases in HIV RNA values (<500 copies/mL). Median CD4 and CD8 T-cell counts were 272 and 554 cell/mm3 at baseline, increasing to 679 and 986 cells/mm3 at week 12, respectively. Mean values and paired t-tests were used for statistical analyses. CYT107 also decreased PD-1 frequency, a marker of T cell exhaustion, in both CD4 and CD8 T-cells at W12 (p=0.008 and p=0.02). The decrease of PD-1 frequency on CD4 T-cells occurred as early as two weeks following the last administration of CYT107 (day 28, 1.8-fold decrease p=0.003).

Twelve patients underwent immunophenotypic analyses of cryopreserved PBMC by flow cytometry at baseline and at week 12. A sustained increase of the gut homing receptor alpha 4 beta 7 integrin frequency
on peripheral CD4 and CD8 T-cells was noted (1.4-fold in both) as early as day seven post first CYT107 administration (t test; p < 0.002), with a peak increase at day 14 (p=0.0001). At week 12 alpha 4 beta 7 remained elevated on peripheral CD8 (p=0.009) on T-cells.

A subset of 4 patients underwent rectosigmoid biopsies both at baseline and between weeks 10-24. Mucosal gut biopsy analysis showed an increase in both CD4 T-cell frequency (38.85 +/- 9.07 pre vs. 53.08 +/- 11.52 post p=0.0273) and counts (106 CD4/gr tissue: 2.29 +/- 1.15 pre vs. 9.01 +/- 7.85 post p=0.1709).

**Summary of Presentation Results**

The findings in the current study confirm previously reported results in SIV infected monkeys showing the ability of IL-7 treatment to drive T-cells to the gut mucosa and facilitate their expansion [3].

"This observation is a key prospective determinant of IL-7 therapeutic activity in the HIV-INR patient population," said Thérèse Croughs, MD, chief medical officer of Cytheris. "In order to establish long term and stable restoration of CD4 counts in these patients, repopulation of T-cells in the gut is crucial to stopping the cell death induced by residual activation in the GI tract and to restoring local immune surveillance."

In this study, not only did IL-7 confirm its potential for T-cell expansion, but it also showed its ability to send T-cells to the gut mucosa where it triggers local T-cell expansion. Numerous experimental and clinical studies confirm that T-cell reconstitution in the gut is critical for restoring control over the HIV virus.

The study therefore provides further evidence suggesting that administration of IL-7 may have an important effect on immunologic recovery in HIV-infected patients whose HAART regimens have been unsuccessful in restoring CD4 T-cells to a stable level. The sustained immunological efficacy suggests that a short course of IL-7 treatment may provide an important avenue for enhancing the immune system and inducing broad spectrum proliferative activity of CD4 and CD8 T-cells in the blood, lymph nodes and small intestine, a key therapeutic effect in achieving long term disease stability in HIV-infected patients.

**About Recombinant Human 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, South Africa and Taiwan have demonstrated the potential of IL-7 to expand and protect CD4 and CD8 T-cells. Currently, Cytheris is conducting multiple international investigations of IL-7 in HIV, HCV, HBV, post-BMT and cancer. Additional studies include a NIAID/NIH-sponsored trial (ICICLE) in idiopathic CD4 lymphocytopenia (ICL); a cancer vaccine study in children with Ewing’s sarcoma family of tumors or similar genetic tumors sponsored by US National Cancer Institute; and a multi-company/institutional study (EraMune 01) sponsored by ORVACS (the international HIV organization funded by the French Bettencourt Schueller Foundation) aimed at attacking the HIV viral reservoir.


**Other Routes to HIV Drug Assistance**

*Los Angeles Times*, (02.28.2011) Francesca Lunzer Kritz

About one-third of US HIV/AIDS patients, more than 160,000 people, rely on AIDS Drug Assistance Programs for their antiretrovirals (ARVs) and related medications. ADAPs are run by individual states, largely with funds supplied by the federal government. But the federal contribution has fallen to 49 percent of ADAP’s cost, down from 72 percent in 2005, and states have been unable to make up the difference. Concurrently, demand for ADAP assistance has grown—thanks to factors including longer patient lifespans, higher drug costs, the poor economy, and federal guidelines recommending earlier treatment. Estimates suggest the program is underfunded by $126 million to $180 million.
As a result, many states have enacted cost-containment measures, including placing ADAP applicants on waiting lists. The National Alliance of State & Territorial AIDS Directors (NASTAD) reports that as of Feb. 24, 6,704 patients were on ADAP waiting lists.

AIDS advocates are hopeful the US Senate follows the lead of the House, which on Feb. 18 voted to divert $42 million in federal funds to move patients from waiting lists into treatment.

Experts recommend the following steps for persons experiencing difficulty accessing ARVs:

* Apply for ADAP, even if your state’s program has a waiting list. Visit http://hab.hrsa.gov/findcare/statehotlines.htm.

* Wait-listed ADAP patients can request help from Welvista, a pharmaceutical patient assistance program. Visit www.welvista.org.

* Persons neither wait-listed for nor enrolled in an ADAP may be able to access help through the drug industry’s Partnership for Prescription Assistance—visit www.pparx.org or telephone 888–4PPA-NOW—or the non-profit group Needymeds; visit www.needymeds.org.


When HIV Moves Into Nursing Homes

*Toronto Star*, (02.27.2011) Susan Pigg

AIDS experts are increasingly concerned about the prospects of the cohort of gay men who have lived for many years with HIV and now are facing their middle-age or senior years. Many are growing old at a rate 15 or 20 years faster than their uninfected peers and are struggling to cope with age-associated physical and mental ailments. Researchers are studying whether these are the result of the disease itself, the medications used to treat it, or the breakdown of the immune system.

“IT’s not going to be a pretty picture. Most people are alone and suffering with these complications,” said Sean Rourke, executive director of the Ontario HIV Treatment Network. “The health care system and the long-term care system just aren’t designed to handle this, not to mention the stigma and other issues that come into play from being gay.”

Casey House, Canada’s first free-standing HIV/AIDS hospice, is working to help. Representatives have visited nursing homes to educate staffers in the hope of alleviating the stigma and fear confronting residents with HIV. “I think the experience in long-term care is that really strong homophobia exists and [so does] a really strong fear of transmission,” said Karen de Prinse, chief nursing executive at Casey House.

Rourke is researching HIV’s toll on the brain. About half of longtime survivors experience symptoms like depression and forgetfulness. In rare cases, HIV’s attack on the brain breaks down social filters, leading to erratic and inappropriate actions that make it very difficult for patients to live among the general population of nursing care facilities.

“It’s not always possible to integrate people with specific needs in with the frail elderly,” said Christina Bisanz, CEO of the Ontario Long Term Care Association, which is asking the province for a 2 percent budget increase to cover its current costs.

Casey House, where more than half of residents are over age 50, and 30 percent have HIV-related dementia, has proposed a day-health program and a downtown facility that would serve 200 HIV/AIDS patients, in particular offering programs to help them stay healthy at home for as long as possible.

Babies Who Escape HIV Face Other Death Risks: Study

*Agence France Presse*, (02.08.2011)

Infants who are spared HIV from their infected mothers have a four-fold risk of dying from other infectious diseases during their first year, a new study finds.

In a group of 109 HIV-infected and uninfected mothers and their babies in Khayelitsha, South Africa, researchers compared the antibody levels of HIV-exposed but uninfected infants to those who were unexposed to HIV. The uninfected, HIV-exposed babies were shown to have lower levels of antibodies to whooping cough, tetanus, and pneumococcus infections—all of which can be preventable through vaccination. However, these vaccines are not always available in developing countries.

“These infants and children represent a vulnerable group with increased rates of lower respiratory tract infection and meningitis and up to four-fold higher mortality in the first year of life,” the study
authors said. “Altered immune responses might contribute to the high morbidity and mortality observed in HIV-exposed uninfected infants.”

While the number of mother-to-baby HIV infections has dropped dramatically during the past decade thanks to preventive medicines, infectious diseases remain a major killer of children under age five globally. The authors called for more studies of the possible link between lower antibodies and higher death rates, and for improved vaccine delivery in poor countries.

“Among South African infants, antenatal HIV exposure was associated with lower specific antibody responses in exposed uninfected infants compared with unexposed infants at birth, but with robust responses following routine vaccination,” the researchers concluded.


New drug regimens cut HIV spread from mother to infant
NIH findings offer additional safeguard for children of mothers untreated during pregnancy

Pregnant women who are unaware that they have HIV miss the chance for drug treatment that can benefit not only their own health, but could also prevent them from transmitting the virus to their infants. When HIV is not diagnosed until women go into labor, their infants are usually treated soon after birth with the anti HIV drug zidovudine (ZDV), to prevent the infants from becoming infected with the virus.

Now, a National Institutes of Health study has found that adding one or two drugs to the standard ZDV treatment can reduce the chances by more than 50 percent that an infant will develop an HIV infection.

The study results were presented on, March 2, at the 18th Conference on Retroviruses and Opportunistic Infections, in Boston. The study was conducted at research hospitals in Brazil, South Africa, Argentina, and the United States, under contract to the NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Additional funding was provided by the NIH's National Institute of Allergy and Infectious Diseases.

An estimated one fifth of people in the United States who have HIV are unaware that they harbor the virus. From 100 to 200 infants are born with HIV in the United States each year, many to women who either were not tested in early pregnancy or who did not receive treatment during pregnancy. Internationally, estimates of HIV testing vary, with only 21 percent of pregnant women in low and middle income countries having been tested for HIV during pregnancy.

"To reduce mother-to-child HIV transmission, it’s best to begin antiretroviral treatment during pregnancy," said Heather Watts, M.D., a medical officer in NICHD's Pediatric, Adolescent and Maternal AIDS Branch, and an author of the study. "However, when treatment during pregnancy isn’t possible, our results show that adding one or two drugs to the current regimen provides another important means to reduce the chance for mother-to-child HIV transmission."

At the 19 participating research sites, the NICHD/ HIV Prevention Trials Network 040 study evaluated 1,684 infants born to women whose HIV infections were not diagnosed until they were in labor. The infants were randomly assigned to three groups: those receiving the standard 6 weeks of therapy with ZDV, those receiving 6 weeks of ZDV plus 3 doses of nevirapine (NVP) during the first week of life, and those receiving 6 weeks of ZDV plus two weeks of lamivudine (3TC) and nelfinavir (NFV). The study results showed that treatment with the two and three drug regimens reduced HIV transmission by more than 50 percent.

ZDV, ZDV+NVP, ZDV+3TC+NFV : Proportion with HIV infection at 3 months : 4.9 percent, 2.2 percent, 2.5 percent

"Our results showed conclusively that the two and three drug regimens are superior to the standard treatment with zidovudine," said study chair Karin Nielsen-Saines, M.D., clinical professor of pediatrics in the Division of Infectious Diseases at the David Geffen School of Medicine at the University of California at Los Angeles.
Research shows how bacteria communicate with each other
Says Hebrew University researcher
Jerusalem, March 1, 2011 – A pathway whereby bacteria communicate with each other has been discovered by researchers at the Hebrew University of Jerusalem. The discovery has important implications for efforts to cope with the spread of harmful bacteria in the body.

Bacteria are known to communicate in nature primarily via the secretion and receipt of extracellular signalling molecules, said Prof. Sigal Ben-Yehuda of the Institute for Medical Research Israel-Canada (IMRIC) at the Hebrew University Faculty of Medicine, head of the research team on the phenomenon, whose work is currently reported in the journal Cell. This communication enables bacteria to execute sophisticated tasks such as dealing with antibiotic production and secretion of virulence factors.

Ben-Yehuda's group identified a previously uncharacterized type of bacterial communication mediated by nanotubes that bridge neighboring cells. The researchers showed that these nanotubes connect bacteria of the same and different species. Via these tubes, bacteria are able to exchange small molecules, proteins and even small genetic elements (known as plasmids).

This mechanism can facilitate the acquisition of new features in nature, such as antibiotic resistance. In this view, gaining a better molecular understanding of nanotube formation could lead to the development of novel strategies to fight against pathogenic bacteria, said Ben-Yehuda.

Amyotrophic Lateral Sclerosis (ALS) Could Be Caused by a Retrovirus, Study Suggests
ScienceDaily (Mar. 2, 2011) — A retrovirus that inserted itself into the human genome thousands of years ago may be responsible for some cases of the neurodegenerative disease amyotrophic lateral sclerosis (ALS), also known as Lou Gherig's disease. The finding, made by Johns Hopkins scientists, may eventually give researchers a new way to attack this universally fatal condition.

While roughly 20 percent of ALS cases appear to have a genetic cause, the vast majority of cases appear to arise sporadically, with no known trigger. Research groups searching for a cause of this so-called sporadic form had previously spotted a protein known as reverse transcriptase, a product of retroviruses such as HIV, in ALS patients' serum samples, suggesting that a retrovirus might play a role in the disease. However, these groups weren't able to trace this reverse transcriptase to a specific retrovirus, leaving some scientists in doubt whether retroviruses are involved in ALS.

Seeking to verify whether a culprit retrovirus indeed exists, Avindra Nath, M.D., a professor of neurology at the Johns Hopkins University School of Medicine, and colleagues examined brain samples from 62 people: 28 who died from ALS, 12 who died from chronic, systemic diseases such as cancer, 10 who died from accidental causes and 12 who had another neurodegenerative disease, Parkinson's disease, at the time of their deaths. Using a technique known as polymerase chain reaction, the researchers searched for messenger RNA (mRNA) transcripts from retroviruses, a chemical signature that retroviruses were active in these patients.

In samples from the ALS and chronic disease patients, the search turned up mRNA transcripts that came from human endogenous retrovirus K (HERV-K). This retrovirus is one of thousands that became a part of the human genome after infecting our ancestors long ago. Nowadays, these retroviruses are no longer contagious, but are instead passed along through inheritance in part of the genome that scientists consider "junk" DNA.

When Nath and his colleagues took a closer look at the mRNA, they saw that the transcripts seemed to originate from different parts of the genome in the samples from ALS and systemic disease patients. The transcripts also came from different tissues in the brain. While patients with ALS tended to have HERV-K transcripts present in areas surrounding the motor cortex of the brain—the area affected by the disease—the other patients' transcripts were spread more diffusely through the brain.

Although the researchers express caution, the findings, reported in the January Annals of Neurology, suggest that HERV-K might be the ALS retrovirus that researchers have been looking for.

"This paper doesn't establish causation beyond the level of doubt, but it does provide some promising links between HERV-K and ALS," Nath says. "We've never found a putative retrovirus for this disease before, so this opens up a whole new area."

He and his colleagues plan to study whether HERV-K might cause neuronal damage, a step closer to linking this retrovirus to ALS. They also plan to study what factors may cause HERV-K to reactivate in some people and lead to ALS symptoms. Researchers might eventually be able to fight ALS, Nath adds, using antiretroviral drugs specific to HERV-K.
HIV Vaccine Impacts the Genetic Makeup of the Virus

ScienceDaily (Mar. 2, 2011) — An AIDS vaccine tested in people, but found to be ineffective, influenced the genetic makeup of the virus that slipped past. The findings suggest new ideas for developing HIV vaccines.

The results were published Feb. 27 in Nature Medicine.

This is the first evidence that vaccine-induced cellular immune responses against HIV-1 infection exert selective pressure on the virus. "Selective pressure" refers to environmental demands that favor certain genetic traits over others.

The senior author of the multi-institutional study is Dr. James I. Mullins, University of Washington (UW) professor of microbiology. The research team analyzed the genome sequences in HIV-1 isolated from 68 newly infected volunteers in the STEP HIV-1 vaccine trial. Mullins and the other principal researchers who carried out this study were not involved in the STEP trial.

The STEP trial was a double-blind, Phase 2B test-of-concept of a Merck HIV-1 subtype B vaccine. The vaccine, MRKAd5, was designed to make the body produce infection-fighting white blood cells, commonly called killer T-cells, that could recognize and target specific parts of HIV-1 known as Gag, Pol and Nef.

The STEP trial was conducted at 34 North American, Caribbean, South American and Australian locations where the HIV-1 subtype B was the predominant virus in the local HIV-infected populations. The trial enrolled 3,000 participants.

Preliminary tests indicated the vaccine was encouraging the appearance of the desired virus-attacking cells. More than 75 percent of vaccinated participants produced HIV-1 specific T cells.

Nevertheless, this response to the vaccine did not predict protection. The trial failed. Immunizations were halted, Mullins recalled, after the first interim analysis indicated that the vaccine neither prevented HIV-1 infection nor reduced the load of virus in the body.

"Even though the T-cell responses were not sufficient to prevent infection," Mullins said, "we were interested in whether the vaccine-elicited T-cells had any impact on those strains of HIV-1 that established infections in the study subjects."

The research team tested for a "sieve effect," which, Mullins explained, occurs when a vaccine successfully blocks some strains of virus and not others. The researchers wanted to know, What are the genetic characteristics of those breakthrough viruses that slipped past the immunization barrier erected by the MRKAd5 vaccine?

The research team isolated strains of HIV-1 from both vaccine and placebo recipients in the study, and compared the genetic sequences of the strains. This would help researchers to determine if any changes in the "founder virus"—the virus first detected in the infection—might have helped it evade the vaccine-induced immune response and take hold in the vaccinated individuals.

The researchers identified potential T-cell targets in the protein-producing regions of the founder virus genetic sequences and compared these to the virus protein-targets of the vaccine—Gag, Pol and Nef. The researchers found that the distances for these viral genetic sequences were greater for the viruses taken from the vaccinated individuals, compared to those from the placebo recipients.

The most significant virus genetic site distinguishing vaccine from placebo recipients was in the region known as Gag-84, which was encompassed by several of the viral segments targeted by the vaccine.

Moreover, the researchers said that the extended divergence between the viruses from the vaccinated and the placebo groups was confined only to the sequences for the proteins targeted by the vaccine components (Gag, Pol and Nef) and was not found in other HIV-1 protein sequences. The influence of the vaccine on the virus genotype, Mullins said, was subtle.

Mullins and his team, as well as their collaborators from the STEP trials studies, are doing similar studies of the genetic impact of the Thailand vaccine RV144 on the AIDS virus. The RV144 vaccine was the first to show some probable effectiveness, but its efficacy was not great enough to put it to more general use.

The researchers added that their findings on breakthrough viruses suggest that new vaccines should be designed to put selective pressure on the virus in a controlled manner.
Such a vaccine, Mullins said, should select for genetic mutations in regions of the virus known to be associated with viral control and should avoid selecting for strains that can either escape the immune defense or act as decoys to fool the immune system.

The researchers propose a goal for new designs of vaccines aimed at inducing killer T-cell responses: corner the virus into assuming forms that debilitate it. This would make the infecting virus fitness-impaired—unable to adapt, reproduce in great numbers and cause disease progression.

"Despite the sad results of the STEP trial," Mullins said, "it has provided clues to ways for science to go forward in the search for an HIV vaccine."

**Journal Reference:**

**Is HIV drug resistance spreading? Early warning signals say 'yes'**
Keith Alcorn
Published: 03 March 2011
Signals warning of the transmission of drug-resistant HIV are growing in low- and middle-income countries, and governments should step up surveillance efforts as they scale up treatment, experts concluded today at the Eighteenth Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

A World Health Organization (WHO) survey of ‘early warning indicators’ – levels of performance that treatment services should be hitting in order to minimise the risk of drug resistance – showed substantial problems with drug stock-outs, loss to follow-up and patients picking up drugs on time in nine African countries in 2008.

Research by PharmAccess, a Dutch foundation that provides HIV treatment services for the private sector in sub-Saharan Africa, shows that levels of transmitted drug resistance across eleven countries showed that the risk of identifying transmitted drug resistance increased by 38% for each year that a country had been scaling up antiretroviral treatment.

Furthermore, a survey of recently infected young people in Kampala, Uganda, showed that 8.6% had evidence of drug-resistant virus, with resistance to all three classes of antiretroviral drug currently available in the country detected among the sample.

In Latin America, rates of transmitted drug resistance may run as high as 20% in some parts of Brazil, and 6.8% in Mexico, researchers reported.

**Transmission of drug resistance**
Viruses resistant to drugs used in HIV treatment may be transmitted by people on treatment that is failing, or by people who have stopped or interrupted treatment. The best way of preventing the transmission of drug-resistant virus, apart from consistent condom use during sex, is to ensure that doses of medication are never missed.

However, interruptions in drug supply and difficulties in reaching the clinic to pick up drugs, often due to poverty or fluctuating income, mean that even patients with good adherence to treatment may be blocked in their efforts to take medication consistently.

For this reason the World Heath Organization developed a set of early warning indicators that are being monitored at a large sample of HIV clinics in sub-Saharan Africa, in order to give advance notice of problems, and to provide feedback to clinics on how they are doing.

**Early warning indicators**
A review of clinic performance in sub-Saharan Africa in 2008 found that in respect to indicators most likely to affect adherence, clinics needed to improve substantially to minimise the risk of resistance.
Early warning indicators
Survey of 130 clinics in 9 countries, 2008

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<tr>
<th>Indicator</th>
<th>Proportion of clinics reaching target</th>
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<tbody>
<tr>
<td>100% prescription of WHO first-line recommended regimens</td>
<td>86%</td>
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<tr>
<td>&lt; 20% loss to follow-up</td>
<td>43%</td>
</tr>
<tr>
<td>&gt;70% retention on appropriate first-line regimen</td>
<td>42%</td>
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<tr>
<td>&gt;90% of patients picking up prescribed ARVs on time</td>
<td>17%</td>
</tr>
<tr>
<td>&gt;80% of clinic appointments attended as scheduled</td>
<td>55%</td>
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<tr>
<td>100% of drugs available at pharmacy at all times</td>
<td>42%</td>
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PharmAccess carried out a review of drug resistance in 2478 treatment-naive patients commencing antiretroviral treatment at 13 sites in eleven countries, and found an overall prevalence of 5.71% (95% confidence interval 4.82 to 6.70%). Resistance to all three drug classes was found (NRTIs 2.2%, NNRTIs 3.41% and PIs 1.27%). The presence of resistance at a site was significantly associated with the time since the initiation of ART provision in that geographic area (odds ratio 1.56, p<0.001). The researchers calculated that the risk of resistance increased by 38% for each year of ART provision.

A survey conducted in 2009 and 2010 in Kampala, Uganda, which sought to identify young people recently infected through voluntary counselling and testing centres, found an apparent increase in transmitted drug resistance when compared to a sample of young women tested through antenatal clinics in 2007. Although the level of resistance identified was somewhat higher than the 2007 sample, at 8.6%, the researchers said that the prevalence of resistance was still low to moderate.

Nevertheless, they say it is time to step up resistance surveillance in Uganda.

Resistance surveillance in Brazil using dried blood spot sampling and testing through a central laboratory showed large regional variations, with prevalence of transmitted resistance as high as 19.9% in Salvador province and 12.8% in Rio de Janeiro.

Unlike in Africa, where the predominant form of transmitted drug resistance is non-nucleoside reverse transcriptase inhibitor resistance relating to use of nevirapine and efavirenz, resistance in Brazil is more likely to be related to use of nucleoside analogues, and may reflect the past use of unboosted protease inhibitors, leading to greater emergence of NRTI resistance when those regimens failed.

References
1. Hamers R et al. HIV-1 drug resistance in ARV-naive individuals in sub-Saharan Africa is associated with time since scale-up of ART. Eighteenth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 622, 2011.

Forecasters agree PrEP/microbicides could cut HIV infections in South Africa
Gus Cairns
Published: 03 March 2011
Several presentations at the Eighteenth Conference on Retroviruses and Opportunistic Infections this week used mathematical modelling to forecast the impact of adopting oral pre-exposure prophylaxis (PrEP) or a topical microbicide in a high-prevalence country, added to HIV treatment or on its own. Three used South Africa as a model, while one analysed how PrEP might affect a serodiscordant couple.

In this piece we look at the first two models, which look at how PrEP/microbicides might affect HIV incidence and prevalence. The other two models looked at cost-effectiveness (see Modellers examine the cost-effectiveness of PrEP in Africa).

PrEP's effect on prevalence
Ume Abbas from the Cleveland Clinical Foundation modelled the effect of increased antiretroviral provision with or without additional oral PrEP in South Africa.

She used an optimistic scenario for the expansion of HIV treatment, assuming that antiretrovirals (ARVs) would eventually reach 80% of people with a CD4 count below 200 cells/mm³. She assumed...
various mortality, dropout and treatment failure rates, and also assumed that, in line with the Partners in Prevention study, that suppressive ARV treatment would cut people’s infectiousness by 92%.

This expansion of treatment alone would prevent 696,000 new HIV infections up to the year 2022. However, there would also be 295,000 cases of drug resistance (8.5% of 3.4 million on treatment, a third of it due to transmitted resistance).

She then assumed that PrEP for HIV-negative people was substituted for antiretroviral treatment for people with HIV. This is not a scenario likely to be adopted. If it was, though, it would prevent 200,000 new HIV infections, and there would be a lot less drug resistance (24,500 new cases or 1.1% of 2.2 million on PrEP).

If both ARV treatment and PrEP on this basis were introduced, 839,000 HIV infections would be prevented (20% more than with treatment alone), and there would be 323,000 cases of drug resistance (9.5% of 3.4 million on treatment and PrEP).

This was on the basis of a realistic model of PrEP based on levels achieved in the iPrEx study: the model parameters were that PrEP would reach 50% of those in need of it within five years from now, that it would have 50% efficacy, that people would only take it half the time, and that the average length of time on PrEP would be five years.

With a more optimistic PrEP scenario where it had 70% efficacy, adherence was 80% and people stayed on it for ten years, 1.25 million infections would be averted.

**A microbicide’s effect**

Valentina Cambiano and a team from University College London modelled the effect of a continued, slow scale-up of HIV treatment with a tenofovir gel microbicide added for women. It was assumed that the gel would have the same efficacy as that seen in CAPRISA 004 and the same adherence characteristics would apply: 40% of the women would use it more than 80 of the time, 40% less than 50% of the time, and the other 20% between 50 and 80% of the time. They assumed that 70% of women in need would have access to tenofovir gel by 2015. Scale-up of ARVs was similar to the Abbas paper, with 65% of people with HIV diagnosed by 2025 and 70% of them on ARVs (45% of all HIV-positive people).

If this scale-up continues but a microbicide is not introduced, the model finds that HIV incidence in the adult population would be 1.13% a year in men and 1.48% in women by 2025. If a microbicide is added, then incidence in men would be 0.85% a year and 0.81% in women. Altogether there would be 32% fewer infections between 2012 and 2025 if a microbicide was used.

**References**


**Partners study expands our knowledge of HIV transmission risk**

Gus Cairns

Published: 03 March 2011

A prevention study in which the intervention being tested failed is turning out to be a fertile source of information about HIV transmission risk in heterosexuals.

Three substudies from the Partners in Prevention (PinP) prevention trial presented at the 18th Conference on Retroviruses shed more light on the risk of transmission at specific viral load levels, how genital viral load influences infectiousness, and whether the viral load in the partner who transmits HIV influences viral load in the one who is infected.

PinP involved 3297 serodiscordant couples. It gave the anti-herpes drug aciclovir to the partners with HIV, all of whom also had the genital herpes virus HSV-2, to see if this would reduce the chance of their transmitting HIV to their HIV-negative partner. It did not, but HIV treatment, which was started by 349 of the HIV positive partners during the study, did, reducing the likelihood of transmitting HIV by 92%.

**Blood plasma viral load and infectiousness**

James Hughes of the University of Washington in Seattle (UWS) presented findings on the relationship between HIV viral load in blood and the chance of transmission.

There were 151 new HIV infections during the two-year study, 108 of them originating from the main partner, as determined by phylogenetic analysis of their viruses. For this substudy, 86 linked transmissions with full viral load data from the transmitting partner were included.
The HIV positive partner of each couple had their viral load tested every three to six months during the study and the HIV negative partner took an HIV test every three months. Each time they came to the study centre they were asked about their sexual behaviour since the previous visit.

Of note, there were 56 transmissions between partners where 100% condom use was claimed (the majority of couples in PinP said they used condoms) and 15 in couples who claimed to have had no sex since the last visit.

The risk of HIV transmission per sex act derived from these figures was one per 526 sex acts from men to women, and one per 1000 from women to men. The male-to-female risk was higher because transmitting men tended to have a higher viral load and infected women were more likely to have herpes and be younger. Adjusting for these factors produced a roughly equal risk of transmission regardless of the sex of the transmitting partner.

Each tenfold increase in viral load in the transmitting partner multiplied the risk of infection 2.8-fold. This may be summarised as follows:

<table>
<thead>
<tr>
<th>Viral load in transmitting partner</th>
<th>Per-act infection risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>One in 3571</td>
</tr>
<tr>
<td>10,000</td>
<td>One in 1220</td>
</tr>
<tr>
<td>100,000</td>
<td>One in 434</td>
</tr>
<tr>
<td>1,000,000</td>
<td>One in 149</td>
</tr>
</tbody>
</table>

There was an 18% lower risk of transmission per every five years older in the HIV-negative partner.

HSV-2 in the HIV-negative partner more than doubled the risk of infection, and genital ulcer disease more than tripled it. Circumcision, if the negative partner was a man, halved his risk of infection – roughly in line with the circumcision trials – and self-reported 100% condom use made transmission 78% less likely, also in line with other meta-analyses of condom use.

### Genital viral load and transmission

Having said this, viral load in semen and vaginal fluids probably influences the risk of transmission more than blood plasma viral load. Jared Baeten, also from UWS, presented a substudy of 2521 of the HIV positive partners which measured the viral load in cervical swabs from the women and in semen from the men, and related them to the chance of transmission.

Cervical samples from 1805 women, including 46 who transmitted HIV to their partner, and semen samples from 716 men, including 32 who transmitted HIV, were tested.

Each tenfold increase in genital viral load was associated with a 2.2-fold increase in the likelihood of transmission by women, and a 1.8-fold increase in the likelihood of transmission by men, roughly in line with the results from James Hughes's study above.

After adjusting for blood plasma viral load, genital viral load was independently associated with the risk of transmission. What this means is that if we discount the influence of blood plasma viral load, there was still an additional 70% increased risk in the chance of transmission per tenfold increase in genital viral load. This suggests that genital viral load is, as anticipated, a better guide to the likelihood of transmission than viral load in blood.

Of note however, genital viral load is more often undetectable, and there were seven female-to-male and four male-to-female HIV transmissions from people with undetectable genital viral load but detectable HIV in their blood. There were no transmissions from someone with an undetectable viral load in blood and detectable genital viral load.

### Relationship between partners’ viral load

Finally, Jairam Lingappa of UWS presented findings that showed there was a link between the viral load in the transmitting partner and the eventual viral load in chronic infection (the viral 'set point') in the infected partner. This has already been shown to apply in studies in gay men.

This has important implications for treatment as prevention as it may mean that if people with low viral loads on treatment do nonetheless transmit HIV, viral load could be lower and disease progression slower in those infected.

A substudy of 101 linked transmission pairs, where it could be shown that the primary partner passed on HIV to their negative spouse, showed that for each tenfold increase in the blood plasma viral load in the transmitting partner there was a 2.5-fold increase in the viral load set point in the infected partner—very similar to the per-act increase in the chance of infection per tenfold increase in viral load.

If the transmitting partner took aciclovir rather than placebo, then their average viral load was 45% lower and the set point in the infected partner was 60% lower.
In cases where the source partner was a circumcised man, then the average viral load in the infected women was 80% lower.

Lingappa also looked at the transmissions that came from non-primary partners and found that there was a mysterious correlation between viral load in the primary partner – even though they were not the source of the infection – and the infected partner’s viral load. For each tenfold increase in the primary partner’s viral load, the infected spouse’s set point viral load doubled.

Lingappa speculated that immune reactions to regular partners with high viral loads might make people more susceptible to infections by unfamiliar viruses.

He also found that pregnancy posed a big additional progression risk for women infected by non-regular partners; their viral load set point was 14 times higher than in other people.

References

More US Youth Say They Are Not Having Sex

Reuters, (03.03.2011)
The largest and most in-depth report on US sexual behavior, sexual attraction, and sexual identity shows a rising number of young people are electing to remain abstinent. In 2006-2008, 29 percent of females and 27 percent of males ages 15-24 reported not having any sexual contact, compared with 22 percent in 2002, CDC said Thursday.

National Center for Health Statistics researcher Anjani Chandra, PhD, and colleagues used data based on computer-assisted interviews with 13,495 males and females ages 15-44. That 2006-2008 National Survey of Family Growth data was compared with results from the 2002 NSFG and other national surveys. The team found few overall changes in the nation’s sexual patterns compared to the 2002 survey. But for the first time, they examined certain, specific behaviors that young people may not always report as sex because it is not vaginal intercourse.

“This focused look at oral and anal sex among teens and young adults is prompted by concerns that some young people may engage in other types of sexual contact before they have vaginal intercourse, to avoid the risk of pregnancy,” the researchers explained. “In addition to placing themselves at risk of [STDS], some studies have documented that engaging in these other types of sexual contact may hasten young people’s initiation of vaginal intercourse.”

Among teenagers ages 15-19, 7 percent of females and 9 percent of males reported oral sex with an opposite-sex partner but no vaginal intercourse. Of sexually active people ages 15-24, almost 63 percent of females and 64 percent of males had oral sex, versus almost 69 percent in 2002. Around 21 percent of young males said they had had anal sex, compared to 22 percent in 2002, while the number of young females reporting anal sex remained unchanged at about 20 percent.

Twice as many females reported any lifetime same-sex contact, 13 percent versus 5.2 percent for males.

“These data are relevant to demographic and public health concerns, including fertility and [STDS] among teenagers and adults,” the researchers noted.


Female Condoms Are Gaining Ground

USA Today, (03.03.2011) Rita Rubin
First approved by the Food and Drug Administration (FDA) in 1993, the female condom was slow to gain acceptance. Now, however, the improved version, dubbed FC2, appears to be making headway.

The number of FC2s distributed in the United States last year tripled, said Mary Anne Leeper, founder of its manufacturer, the Female Health Company. The product now is sold in more than 100 nations, and it even has fans on Facebook.
On Valentine’s Day, the San Francisco Department of Public Health handed out free FC2s in several neighborhoods. Also that week, Walgreen’s stocked three-packs of the condoms, priced at $6.99, in about 10 percent of its 7,600 stores, many in cities with high HIV burdens.

In Chicago, New York City, and New York state, health departments are partnering with non-profits to distribute FC2s to women as well as to men who have sex with men, although data about the device’s safety and efficacy for anal sex are lacking.

All 55 CVS stores in Washington carry the FC2, priced at $6.49 for a three-pack, and last year 25,000 people there used it, Leeper said.

Whereas the original female condom was made of polyurethane, the improved version, approved by FDA in March 2009, is seamless and made of more comfortable synthetic latex.

Church Leader Reverses Stance on HIV, Reaches Out to Those Affected

For Kenyan church leader Patrician Sawo, discovering she herself had HIV marked the beginning of a turnaround in her attitude about the virus and those it affects.

“I thought it was a moral issue and a punishment for the disobedient,” Sawo said. But in 1999, she discovered she was HIV-positive; she suspected the transmission resulted from a blood transfusion. Despite four years fasting and praying for healing, she remained infected. She and her husband lost their jobs and were evicted from their home. A small business they started failed, too; customers were afraid to be around them.

At last, Sawo found her way to the non-governmental organization Handicap International, learned more about HIV/AIDS, and began to get her life back.

Ordained a minister in 2002, Sawo helped found ANERELA+, an organization of African religious leaders affected by HIV/AIDS. Sawo threw herself into her AIDS ministry, using nearly all her income to help those who came to her for assistance.

Sawo and her husband in 2005 established the Discover to Recover Center. As its patients died, the center evolved into a home for the orphans they left behind. Sawo is assisted by seven staff members and several of her own children in caring for the center’s 48 young residents. She also provides support for about 50 HIV-affected children who live with family members, and she counsels some two-dozen people monthly.

Sawo’s husband died of malaria and typhoid in 2009; the center survives chiefly with support from the US non-profit Hope Span. She hopes eventually to expand the center’s services to include primary and secondary schools, as well as vocational training. And Sawo believes that through her work, she has found the “healing” she prayed for when first diagnosed.

For more information, visit http://hopespan.org/discover_to_recover_centre.htm.

CROI: Five-Drug HIV Therapy No Better than Standard

Boosting the number of antiretrovirals (ARVs) administered to treat acute and early HIV infection is not effective, according to a study presented at this week’s 18th Conference on Retroviruses and Opportunistic Infections in Boston.

Forty-eight weeks into the 96-week study, patients receiving five drugs had equivalent amounts of HIV RNA in their blood compared to those receiving standard three-drug therapy, and there also was no difference in a range of other immune system measurements, said Martin Markowitz, MD, of New York’s Aaron Diamond AIDS Research Center. The results suggest that “upping the ante from the get-go may not work,” he said.

Markowitz and colleagues enrolled 40 early-stage HIV patients and randomly assigned them, in a one-to-two fashion, to receive either three or five medications.

In the three-drug arm, 14 patients took a fixed-dose combination of the reverse transcriptase inhibitors tenofovir and emtricitabine (Truvada) and a boosted protease inhibitor—either atazanavir (Reyataz) or darunavir (Prezista).

In the five-drug arm, 26 patients received the same drugs plus the entry inhibitor maraviroc (Selzentry) and the integrase inhibitor raltegravir (Isentress).

“We measured pretty much everything that can be measured, and to make the story rather simple, we did not see any substantial or significant differences,” Markowitz said.

Thirty-four patients remained in the study. Among results at 48 weeks:
While the five-drug patients achieved undetectable HIV RNA levels more rapidly than the three-drug patients, by 24 weeks there was no significant difference in the proportion with undetectable virus.

In both study arms, patients had strong recovery of CD4+ cells of about 300 each; there was no significant difference between the groups.

No differences were found in levels of proviral DNA or cell-associated HIV RNA, or their rates of decay over time.

No differences were found in levels of naïve and total CD4 cells or immune system activation markers.

All three patients who had virological failure were in the five-drug group.

Scott Hammer, MD, chief of infectious diseases at New York-Presbyterian/Columbia University Medical Center, said the results comport with those of "study after study." "You can intervene with antiretrovirals, you can drive the [HIV] RNA down, but there's an irreducible minimum you can't get below," Hammer said. Very early on in the course of infection, HIV seems to establish a reservoir that is unaffected by current treatments, he said.

No More Science Fiction—HIV Gene Therapy Delivers

SUMMARY: A gene therapy technique using a zinc finger nuclease to disable expression of CCR5 co-receptors on CD4 cells led to robust T-cell increases in a small study reported at the 18th Conference on Retroviruses and Opportunistic Infection (CROI 2011) this week in Boston. A related study showed that a similar technique can knock out CXCR4 co-receptors. Trial participant Matt Sharp describes the study findings and his experience.

By Matt Sharp

In what could be considered a scientific breakthrough in HIV research, gene therapy trials provided a buzz of excitement at an otherwise typical HIV/AIDS conference.

Jay Lalezari from Quest Clinical Research in San Francisco presented findings from a small Phase 1 clinical trial at a Monday session looking at "Innovative Therapeutic Approaches." A companion trial at the University of Pennsylvania was presented by Carl June at a closing session entitled "Obstacles to a Cure."

They manipulated using zinc finger nucleases, which act like small molecular scissors, blocking expression of the CCR5 co-receptor on CD4 cells. This co-receptor is necessary for many strains of HIV to attach to and fuse into a CD4 cell, beginning its lifecycle of destruction. Other HIV strains use an alternate co-receptor called CXCR4.

Lalezari presented data on the altered CD4 cells—known as SB-728-T—in 6 men who have been living with AIDS for over 20 years. Participants had continued low CD4 cell counts, ranging from 200 to 500 cells/mm³, despite having undetectable HIV viral load on antiretroviral therapy.

The study procedure involves removing blood from participants in an apheresis clinic. CD4 cells are extracted and processed with the zinc finger technology, disrupting the CCR5 gene. The altered cells are allowed to multiply and the new cells are then frozen and sent to the study clinic, where they are thawed and re-infused back into the participant in about 20 to 30 minutes.

Although the study was small, 5 of the 6 participants in the first 2 cohorts had an average increase of 200 CD4 cells/mm³ during 1 year of follow-up after the infusion. The procedure was safe and well tolerated. One participant did not respond, most likely due to a lower baseline CD4 count.

About 25% of the donated cells had the CCR5 co-receptor removed, and when re-infused, 3%-6% of those cells remained present after 3 months. Showing that the treated cells can reach other areas of the body, rectal biopsies revealed that the cells migrated to the gut mucosa, which is an important HIV hiding place.

The motivation for this CCR5 deletion approach came from the successful treatment of Timothy Brown, also known as the "Berlin patient." Brown, living with AIDS and leukemia, received 2 bone marrow transplants from a donor with CD4 cells that were naturally deficient in CCR5 co-receptors due to
an uncommon genetic mutation. Four years later, he is considered cured of AIDS and his leukemia is in remission. His case has spawned a new wave of HIV research that hopefully will lead to what is now characterized as a "functional cure."

There is a licensed antiretroviral drug that targets the CCR5 co-receptor—maraviroc (Selzentry)—but the gene therapy approach is an advance in improving the quality of life in people with HIV, who at this point need to take drugs the rest of their lives.

Sangamo BioSciences, a small biotech company in Richmond, California, holds the patent for SB-728-T and is also working with zinc finger nucleases in other disease areas. At CROI researchers from the University of Pennsylvania and Sangamo presented further work on manipulating the gene for CXCR4, the other important co-receptor for HIV. They hope to use both CCR5- and CXCR4-deleted cells in a combination approach.

This writer enrolled in the San Francisco trial, and I must admit it was thrilling to see my own data presented at CROI. I have been seeking a treatment that would boost my immune system, since I have not been able to increase my CD4 cells for over 20 years on antiretroviral therapy. In October, when I received the first lab report, I was stunned to see the positive results. My T-cells had doubled and I experienced no side effects. Despite the unknowns of entering a Phase 1 gene modification trial, I recognize that much of the success of my HIV treatment history has happened because I chose to take risks along the way.

While it is important to understand that this research is far from being a cure for AIDS, the trial is a critical step in opening the minds of the cynics who refuse to believe a cure is attainable. Scientists and funders may also recognize that the ship has left the dock, and they may not want to miss a golden opportunity to help end the epidemic of our time. 3/4/11

1. References


New microscope produces dazzling 3-D movies of live cells
A new microscope invented by scientists at Howard Hughes Medical Institute’s Janelia Farm Research Campus will let researchers use an exquisitely thin sheet of light—similar to that used in supermarket barcode scanners—to peer inside single living cells, revealing the three-dimensional shapes of cellular landmarks in unprecedented detail. The microscopy technique images at high speed, so researchers can create dazzling movies that make biological processes, such as cell division, come alive.

The technique, called Bessel beam plane illumination microscopy, is described in a research article published online on March 4, 2011, in the journal Nature Methods.

A major goal of biologists is to understand the rules that control molecular processes inside a cell. If one is trying to learn the rules of a game, it is better to have a movie of people playing the game than it is to have still photos — and the same is true for cells, says Janelia Farm group leader Eric Betzig. He has been inventing and improving microscopes for more than 30 years. Despite having seen huge advances in microscopy during that time, Betzig says the field is still hindered by the fact that many microscopy techniques require that cells be killed and fixed in position for imaging. There is only so much one can learn from studying dead cells — the equivalent of still photos, he says.

Betzig wanted to create a microscope that would let researchers see the dynamic inner lives of living cells. The notion of studying live cells, stippled with fluorescently labeled proteins and other molecules, is not new. But live-cell techniques can be problematic because light produced by microscopes can damage the cell over time. Besides cell damage, light causes the fluorescent molecules —of which there are only so many—to wink out over time. In other words, the longer you study the cell to uncover its properties, the more damage you do to the cell and the more likely you are to spend your "photon budget," Betzig says.

What’s more, the light of a microscope exposes more of the sample than just the small portion that is in focus. Illuminating the out-of-focus regions produces blur, making small intracellular features appear as lengthened blobs rather than sharp dots. "The question was, is there a way of minimizing the amount of damage you’re doing so that you can then study cells in a physiological manner while also studying them at high spatial and temporal resolution for a long time?" Betzig says.
Long before arriving at Janelia Farm in 2006, Betzig began thinking about ways to improve live-cell microscopy. He put those thoughts on hold while he focused on designing new microscopy techniques that would ultimately shatter the limits of spatial resolution (imposed by the laws of diffraction). Until recently, microscopes could see objects no smaller than 200 nanometers in size. Several years ago, Betzig and his Janelia Farm colleague Harald Hess invented photoactivated localization microscopy, PALM, which can produce images of objects only 10-20 nanometers in size.

PALM and most other microscopes—even the ones college students use in their biology classes—work by exposing the sample through one objective lens and then collecting the light that comes back through that same lens. That approach causes light to damage the sample and induces blur, making it difficult to observe live cells.

In 2008, Betzig began working on ways to overcome these challenges. One idea he had was to use plane illumination microscopy. First proposed about 100 years ago, plane illumination involves shining a sheet of light through the side of the sample rather than the top. To do that, microscopists use two different objective lenses that are perpendicular to one another. "Because you come from the side, plane illumination confines the excitation much closer to the part that’s in focus," Betzig says.

Although other researchers, including Janelia Farm Fellow Philipp Keller, have used plane illumination to great effect to study multicellular organisms hundreds of microns in size, the light sheets were still too thick to work effectively for imaging within single cells only tens of microns in size. The main problem is that the wide swath of light used in plane illumination exposed more of the cell than Betzig’s group wanted. This caused excessive blur and light toxicity. To circumvent this problem, his group used a Bessel beam, a special type of non-diffracting light beam studied by physicists in the late 1980s, and used today in applications including bar-code scanners in supermarkets. Sweeping the beam across the sample creates a thinner light sheet, his group found.

Bessel beams behave a bit strangely, though, and this is what has kept Betzig’s postdoctoral researchers—Thomas Planchon and Liang Gao—busy over the past few years. Although they produce a very narrow light beam, Bessel beams also create somewhat weaker light that flanks the focal point, making the pattern of illumination look like a bull’s eye. The extra light lobes are a hindrance because they excite too much of the sample. To compensate for this problem, Betzig’s group used two tricks. The first is a concept called structured illumination, where instead of sweeping the beam continuously, they turned it on and off rapidly, like firing a machine gun. This creates a periodic grating of excitation that can be used to eliminate any out-of-focus blur. (Structured illumination, used by Janelia Farm Group Leader Mats Gustafsson, is also one way of achieving super-resolution.)

Another strategy Betzig’s group used is two-photon microscopy, a method commonly used in neuroscience to visualize thick pieces of brain tissue. One of the advantages of two-photon microscopes is that very little fluorescence signal is generated from weakly exposed regions. Thus, when they applied two-photon methods, the background from the Bessel side lobes was eliminated, and all that remained was the light from the narrow central part of the Bessel beam.

They then set out to image as fast as possible. The Bessel beam sweeps quickly through the sample, allowing the group to take nearly 200 images/second and build three-dimensional stacks from hundreds of two-dimensional images in one to 10 seconds. As they had hoped, they found that they could take hundreds of such three-dimensional image sets without harming the cell, generating amazing movies of cellular processes such as mitosis, where chromosomes divide as one cell becomes two. "There’s no other technique that comes close to imaging as long with such high spatial and temporal detail," Betzig says.

Last summer, as soon as they got their first live cell images, Betzig, Planchon and Gao packed up the new instrument in a rented sport utility vehicle and took it to the Woods Hole Marine Biological Laboratory in Massachusetts for a physiology course, where they worked with co-authors Jim and Cathy Galbraith from the National Institutes of Health. "We learned a lot about what works and what doesn't and ways to treat the cells in a way that maintains their physiological state while we’re doing the imaging," he says. "Like every microscope, the instrumentation is only part of the puzzle. A lot of it is finding the right samples, and right preparation methods to make it work."

The new microscope is also exciting because it may be used in the future to improve super-resolution microscopy. PALM and other super-resolution techniques are limited to looking at thin, dead samples, and can be very damaging when looking at live ones. "That's what's really great about the Bessel—we can confine that excitation and really start to think about applying super-resolution microscopy to study structure or dynamics in thicker cells," says Betzig. Even without super-resolution, Bessel beam plane illumination microscopy will be a powerful tool for cell biologists, Betzig says, since it noninvasively images the rapidly evolving three-dimensional complexity of cells.
Vaccinated children not at higher risk of infections or allergic diseases

May vaccinations put too much strain on or weaken children's immune systems and are therefore harmful? Roma Schmitz and her colleagues from the Robert Koch Institute investigate exactly this research question in the current issue of *Deutsches Ärzteblatt International* (Dtsch Arztebl Int 2011; 108(7): 105-11). Their data are based on the results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS).

In their study, the authors compare the occurrence of infections and allergies in vaccinated and unvaccinated children and adolescents. These include bronchitis, eczema, colds, and gastrointestinal infections.

The evaluation showed that unvaccinated children and adolescents differ from their vaccinated peers merely in terms of the frequency of vaccine preventable diseases. These include pertussis, mumps, or measles. As expected, the risk of contracting these diseases is substantially lower in vaccinated children and adolescents.

6 months of nevirapine prophylaxis for breastfeeding infants reduces transmission by 76% if mother not on ART

Carole Leach-Lemens
Published: 07 March 2011

Extending the use of daily infant nevirapine to six months reduced the risk of breastfeeding mother-to-child transmission by a significant 76% in HIV-positive mothers with CD4 cell counts over 350 and not yet eligible for antiretroviral treatment Yvonne Maldonado reported on behalf of the HPTN 046 study at the Eighteenth Conference on Retroviruses and Opportunistic Infections in Boston last week.

While the risk for infant death was similar in both the nevirapine and placebo arms, approximately two-thirds of all deaths happened after six months of age when most infants had stopped breastfeeding. Cessation of breastfeeding was not controlled for in the study.

Previous study findings showed that daily infant nevirapine (extended-dose nevirapine) given to breastfeeding infants for six (SWEN) or 14 weeks (PEPI-Malawi) or six months (BAN) was more effective in reducing mother-to-child transmission (MTCT) compared to single-dose nevirapine.

In the analysis presented Dr. Maldonado reported on the incremental protective benefits of extended-dose nevirapine to six months directly compared to six weeks.

In resource-poor settings MTCT continues to cause significant death and disease. Approximately one third of the estimated 450,000 children infected each year are infected through breastfeeding. Safe alternatives are often not feasible for the majority of women in such settings. The risks for infant death and disease linked to not breastfeeding are greater than the risks associated with HIV infection.

Infant prophylaxis has proven effective in reducing MTCT. While maternal ART is also effective in reducing MTCT many women, even if eligible (at CD4 cell counts above 350 cells/mm³), are not able to access treatment in resource-poor settings where coverage is severely limited. Those who do access ART often do so late in pregnancy. Viral suppression can take several weeks. So it is critical to look at the role of infant prophylaxis in reducing MTCT associated with breastfeeding.

HPTN 046 was a randomised, placebo-controlled, double-blind trial undertaken in South Africa, Tanzania, Uganda and Zimbabwe.

The multi-site study began in March 2007 with enrolment completed in January 2010. For the first six weeks of life all infants received single-dose nevirapine.

1522 breastfeeding, uninfected infants born to 1505 mothers were randomised at six weeks of age to get extended nevirapine (759 infants/752 mothers) or placebo (763 infants/753 mothers) for six months.

At the time of randomisation 29% of mothers were on ART for their own health in each arm (221 in the extended-dose nevirapine and 219 in the placebo). Median maternal CD4 cell counts were 560 cells/mm³ and 528 cells/mm³ in the extended-dose and placebo arms, respectively. At six months the percentages of mothers on ART increased slightly to 31% and 32% in the nevirapine and placebo arms, respectively.

95% of infants were reported to be exclusively breastfeeding at three months; between six and nine months over 90% of all infants stopped breastfeeding. There was no significant difference between the arms.
Extended-dose nevirapine given for six months compared to six weeks of age in mothers on ART at the time of randomisation resulted in a 55% reduction in the infection rate (1.1% in the extended-dose nevirapine arm and 2.4% in the placebo arm).

In those mothers not on ART for their own health (CD4 cell counts over 350) the six-month infection rate was 2.4% (1.4% in the extended-dose arm and 3.4% in the placebo arm, p=0.027).

When treatment stopped at six months the rates of MTCT between six and 12 months were similar in both arms.

There were no significant differences in adverse or serious events between the arms.

Dr. Maldonado concluded that the benefits of extending the daily dose of nevirapine in breastfeeding infants of mothers with CD4 cell counts over 350 cells/mm3 and not on ART was significant in reducing MTCT.

These results, she added “support the benefits and safety of extended infant nevirapine for women who do not yet require ART for their own health [or cannot access it], a group of women relatively unprotected at this time.”

**HPTN 040 study: postnatal antiretroviral prophylaxis for infants (comparing zidovudine to two-drug or three-drug prophylaxis)**

Adding nevirapine (NVP) or nelfinavir (NFV) and lamivudine (3TC) to the standard regimen of zidovudine (ZDV or AZT) halved the incidence of neonatal mother-to-child transmission among formula-fed infants born to mothers not getting antiretrovirals before labour Karin Nielsen-Saines reported at the same session.

Speaking for the HPTN 040/PACTG 1043 study, an ongoing prospective randomised trial in Brazil, South Africa, Argentina and the United States, she noted that only maternal viral load and treatment arm were significant factors associated with transmission.

Taking toxicity and ease of use into account initial findings suggested that the ZDV+NVP combination might be the preferred regimen.

As the study evaluated the efficacy of post exposure prophylaxis in the prevention of intrapartum HIV-1 MTCT, only infants to be formula-fed were enrolled.Breastfeeding by HIV-positive women is contraindicated by Brazilian, Argentinian and United States HIV guidelines. In Brazil formula is provided for six months to all patients. In South Africa, patients who chose not to breastfeed and to use formula feed were eligible for enrolment. Infants were followed for the first six months of life.

Safe and effective formula-feeding is not feasible in most resource-poor settings and is associated with high rates of infant disease and death.

The multi-centre three-arm trial, begun in 2007 for women not on ART during pregnancy primarily because they were not identified as HIV-positive due to poor or absent prenatal care.

Women enrolled into the study were diagnosed through rapid testing during admission for labor and delivery. Women got intravenous ZDV when maternal diagnosis was made during labour. Infants were enrolled into the study within 48 hours of birth, and randomised to three different treatment arms for prevention of intrapartum MTCT.

The primary outcome was infant HIV infection at three months of age among infants not infected at birth.

Among 1684 infants transmission occurred in 3.2% (47) during labour and delivery, 24 (4.9%) of whom were in the ZDV arm 95% CI: 3.3-7.2.

Transmission for those in the ZDV+NVP arm was 2.2% (11) (95% CI: 1.2-4.0, p=0.045 compared to the ZDV arm). And for those in the ZDV+NFV+3TC transmission was 2.5% (12) (95% CI: 1.4-4.3%, p=0.045 compared to the ZDV arm).

However, in the ZDV+NFV+3TC arm neutropaenia (low number of white blood cells) was significantly higher than in the other arms (p<0.001).

In response to a question from the audience Dr. Nielsen-Saines noted the study began in 2001-2002 and the choice of ZDV+NFV+3TC was the best available protease inhibitor-based regimen at the time. The decision was made to continue with this regimen when other options became available.

Dr. Nielsen-Saines concluded that a two or three drug antiretroviral prophylaxis regimen is preferable to standard zidovudine for prevention of mother-to-child transmission during labour and delivery among infants born to HIV positive mothers not on antiretrovirals before labour.

Resistance testing is in process and will inform the choice for best regimen.
Reference
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No Quiet Old Age for South Africa’s Grannies
Inter Press Service, (03.02.2011) Elles Van Gelder
The group Grandmothers Against Poverty and AIDS (GAPA) has around 500 members in South Africa, which has the world’s largest HIV/AIDS caseload. Most women in the group thought their kids would take care of them in old age, but instead they are raising grandchildren whose parents have died of the disease. Of the 1.4 million AIDS orphans in South Africa, some 64 percent are being cared for by their grandparents, usually single grannies.

GAPA was founded in the Khayelitsha township outside Cape Town in 2001. The group provides a setting where they can support each other by sharing their burdens and openly discussing the hardships they face.

“A lot of these grannies have five to 10 mouths to feed from their old-age pension,” said Vivienne Budaza, GAPA’s director. “Their kids are dying like flies.”

Thandiwe Matzinga is a GAPA member in Khayelitsha. Despite her aching joints, the 76-year-old cares for three of her grandchildren: twin 15-year-old boys and a seven-year-old girl. At a local community center, she joins a circle of wrinkled faces to share stories. Three of her nine children have died of AIDS.

“When my neighbors heard that kids of mine died of the disease, they didn’t dare to use the same communal toilet as me,” said Matzinga. Now however, “More and more families around me are hit by HIV/AIDS. There are more and more grannies in the same situation asking for my help.”

Nothemba Mdaka, 71, has raised five grandchildren and now is raising five great-grandchildren. She also is caring for a daughter who soon will likely be her third to die of AIDS. Though initially reluctant to talk to the children about sex, she now takes a different approach. “We need to be open about this,” said Mdaka. “Otherwise this killing disease will never stop.”

Helicobacter Pylori Infection Linked to Decreased Iron Levels in Otherwise Healthy Children
ScienceDaily (Mar. 7, 2011) — Children without previous iron deficiencies or anemia who remained infected with Helicobacter pylori (H. pylori) had significantly lower levels of iron compared to children who had the infection eradicated, according to researchers at The University of Texas Health Science Center at Houston (UTHealth).

"Half of the world's population is infected with H. pylori and most of the individuals are asymptptomatically infected, according to several surveys," said Victor Cardenas, M.D., Ph.D., lead investigator of the study and associate professor of epidemiology at The University of Texas School of Public Health El Paso Regional Campus, part of UTHealth. "What we learned in this study is not only does H. pylori cause iron deficiency anemia and iron-deficiency, but that even among children who do not have these conditions, their levels of iron are lower than otherwise healthy children." The research is published in the March issue of the Journal of Pediatric Gastroenterology and Nutrition.

Researchers investigated the link between H. pylori infection and iron levels in non-iron-deficient preschool and school age children in El Paso and found the infection causes a decrease in the levels of iron in children who do not have anemia or an iron deficiency. The bacterium H. pylori infects the lining of the stomach resulting in chronic swelling of tissue, a condition known as gastritis. H. pylori is also a major cause of peptic ulcer disease and the cause of most cancers of the stomach, according to the World Health Organization.

"Iron is an essential nutrient which supports several body functions and exists in small amounts in the body, but it is also required by bacteria such as H. pylori," said Cardenas. "The infection decreases the body’s natural progression of making iron." According to Cardenas, this is the first study conducted in the contiguous U.S. to examine the role of the infection on the levels of iron levels in asymptomatic children.

Over time markers of iron stored in the body increased in children no longer infected. However, children who remained infected lagged in levels of one marker, serum ferritin, at their six month follow-
The protein serum ferritin measures the amount of iron stored in your body, according to the National Institute of Health.

"Previous research has shown that iron levels correlate with several body functions including brain activity and have well documented long-term health consequences such as increased morbidity and mortality and loss of productivity," said Cardenas. "There is a need to research the long-term consequences of asymptomatic H. pylori infections in those without an iron deficiency because the effect we found could be present among those with normal iron levels."

Cardenas and his team used a previously tested therapy, which consisted of one antacid plus one antibiotic for five days, followed by the antacid plus two antibiotics for another five days. While previous studies resulted in high rates of success in eradicating H. pylori, only half of the children given the active medications in Cardenas' study had their infection eradicated, a disappointing result, he said.

Cardenas questions whether asymptomatic H. pylori infections have any significant health consequences. "We want to further investigate if there is a relation between variations of the bacteria strains and iron in adults," said Cardenas.

Journal Reference:

Life-Saving Blood Test for Fungal Meningitis, a Leading Cause of AIDS-Related Deaths in Developing Countries

ScienceDaily (Mar. 7, 2011) — A new, rapid blood test that could lead to early diagnosis and potentially save the lives of hundreds of thousands of people stricken with fungal meningitis, a leading cause of AIDS-related deaths in developing countries, is getting closer to market with a recent collaboration between the University of Nevada, Reno and Immuno-Mycologics (IMMY) in Oklahoma.

"The ability to quickly identify yeast infection in patients is expected to help in significantly reducing cryptococcal meningitis deaths in resource-limited countries such as those in sub-Saharan Africa," said Tom Kozel, professor of microbiology at the University of Nevada School of Medicine. "Cryptococcosis is a rare form of meningitis among otherwise healthy individuals, but an estimated 600,000 lives are lost to this infection each year in patients with AIDS. Many of these lives could be saved through early diagnosis."

If successful, the new field test to detect cryptococcal antigen will use a drop of blood from a finger-stick or a urine sample to immediately identify the presence of the disease so treatment can begin instantly, rather than having to wait for results to be processed at a lab. The point-of-care product is the result of a collaboration between Kozel and Sean Bauman, president and CEO of IMMY. The product is being developed under a licensing agreement established through the University's Technology Transfer Office and IMMY.

"We developed several antibodies to the fungus with the support of research funded by the National Institutes of Health," Kozel said. "IMMY needed an antibody that worked well with their idea for this new noninvasive procedure to introduce in developing countries where deaths are skyrocketing from HIV-related cryptococcal meningitis. We found fairly quickly that one of ours works very well."

Kozel developed the antibody used for the Cryptococcus test in his lab at the University of Nevada, Reno. Bauman commercialized the technology to make it available at low cost to patients in developing countries through IMMY, a market leader in diagnostics for fungal infections.

"One of the stipulations in our agreement for the licensing of the product with IMMY is to have this crucial test available at low cost," Ryan Heck, director of the University's Technology Transfer Office, said. "Dr. Bauman had already begun to make this happen on several avenues."

IMMY is using the antibody now for testing in Africa, but only through the traditional, time-consuming and expensive methods of venipuncture (blood draw) or spinal tap for cerebrospinal fluid. The team is working to get additional funding for studies needed to further develop and validate the new point-of-care product to make it readily available to patients.

We have submitted a version of the test that is designed for use with serum from a venipuncture or cerebrospinal fluid to the FDA for approval. We have received the CE mark, which allows sales in EU countries and many developing world countries," Bauman said. "We are already manufacturing and distributing the diagnostic for this use."
Modification of the test to a point-of-care format and clinical validation will be a major step toward meeting the World Health Organization’s Global Access health requirements.

"With the point-of-care product, a health-care provider can give the test, observe the results and administer the first dose of oral medication, all within a few minutes," Kozel, who has been conducting AIDS research for more than 25 years, said. "Studies have shown early identification and treatment are essential to beat the disease; a late diagnosis means antifungal therapy will likely fail in resource-limited countries. Most patients in that setting are not diagnosed until they are very sick, and then it’s too late."

Antifungals used to treat cryptococcosis are available for free or at low cost in regions such as sub-Saharan Africa. However, early diagnosis is crucial for successful drug therapy. Bauman saw this need and the staggering numbers of preventable deaths occurring in third-world countries, particularly in Africa, and decided to do something about it.

"As many as one in 10 AIDS patients in countries with limited infrastructure or resources may develop cryptococcal meningitis," Kozel said. "If we can diagnose early and begin treatment, we can save an amazing number of lives."

**Roundworm could provide new treatment for sepsis**

Liverpool, UK—7 March 2011: Research by the University of Liverpool has found that systemic inflammation caused by sepsis can be suppressed by a protein which occurs naturally in a type of roundworm.

Sepsis is a serious inflammatory condition, caused by the body over-reacting to infection. The body becomes overwhelmed by bacteria, setting off a series of reactions that lead to inflammation and clotting. It affects around 20 million people worldwide each year, and accounts for a large proportion of intensive care unit admissions.

For the past 30 years, sepsis has largely been treated by antibiotics and maintenance of blood flow. Despite these treatments—often complicated by antibiotic-induced liver injury or the presence of multi-drug-resistant bacteria—mortality rates for those with severe illness who go into multi-organ damage and septic shock, remain as high as 50%. New treatments for septic shock are of high clinical need.

Findings by an international team, led by Professor Alirio Melendez, based at the University’s Medical Research Council Centre for Drug Safety Science in the Institute of Translational Medicine, show that inflammation triggered by bacterial endotoxins in immune cells from patients with sepsis is suppressed by a protein called ES-62 which is secreted by a type of roundworm called Acanthocheilonema viteae.

Roundworms can infect the human digestive tract, lymphatic vessels, skin and muscle. They are extremely common—particularly in parts of the world with poor sanitation—and it is estimated that nearly a quarter of the world’s population are currently infected. Roundworm can live in the human body for decades without adverse effects or triggering the immune system.

Scientists already know that the protein secreted by roundworm is capable of suppressing inflammation and people infected with worms usually benefit from reduced inflammation if they suffer from conditions such as allergies and autoimmune diseases.

Professor Melendez explained: ‘The protein secreted by the roundworm stimulates a process called autophagy, a process of ‘self-eating’ that is essential to clear damage to cellular proteins or organelles and promote cell survival and function during stress situations.

“Autophagy reduces inflammation but at the same time permits the clearance of microbial infection. The findings suggest that ES-62 could be used to induce autophagy and reduce the overwhelming inflammation that is responsible for the massive tissue damage seen in sepsis.”

He added: “ES-62 has the therapeutic ability to enhance recovery in septic shock by suppressing and limiting catastrophic inflammatory responses while allowing for bacterial clearance to occur. Administration of ES-62, or a synthetic small molecule derivative, alone or in combination with antibiotics could potentially be used treatment of septic shock as well as other inflammatory diseases.”

The research is published in Nature Immunology and was carried out in collaboration with colleagues from the Universities of Strathclyde, Glasgow and the National University of Singapore.

**Cancer in HIV-positive patients**

Most HIV-positive patients die of cancer. In the latest issue of Deutsches Ärzteblatt International (Dtsch Arztebl Int 2011; 108[8]: 117–C), Manfred Hensel’s research group presents epidemiological data.

The authors surveyed all German hospital outpatient clinics and ambulatory care centers specializing in the treatment of HIV patients in the period from 2000 to 2007 and were thus able to analyze the largest collection of data on the incidence of cancer in HIV patients ever assembled in Germany. It first
became clear in the early 1980s that HIV infection is associated with malignancies. Kaposi sarcoma, cervical cancer, and non-Hodgkin's lymphoma were found particularly often in immune-deficient populations. These "AIDS-defining" tumors have since become less frequent, but other types of cancer such as anal carcinoma, Hodgkin's lymphoma, lung cancer, and skin cancer are coming to the fore. Because most patients infected with HIV die of these malignancies, the authors recommend tumor screening for HIV-positive persons.

http://www.aerzteblatt.de/v4/archiv/pdf.asp?id=81038

Experts Develop Tool to Predict Course of Haiti’s Cholera Outbreak, Offer Disease Control Strategies for Immediate Implementation

ScienceDaily (Mar. 7, 2011) — A new study being published early online in Annals of Internal Medicine, outlines the path of the cholera outbreak in Haiti and identifies immediate strategies for controlling the epidemic. Control strategies are needed, as Haiti is in the midst of a cholera epidemic that has killed 4,000 people, and sickened at least 217,000 more in all of Haiti's ten geographical “departments.”

Researchers used publicly available data to produce a “gravity” model to predict the spread of cholera between Haiti’s regions based on the population of the departments and the distance between them. The model also assessed the impact of two distinct interventions: limited-scale vaccination and provision of clean water at the same scale. Through an optimized vaccination scheme to 500,000 individuals, the researchers predict a three percent risk reduction of infection—about twice the risk reduction clean water.

"Given the potential for thousands of additional cholera cases in Haiti, and the high case-fatality rate, a reduction of even a few percent in total case counts will translate into a substantial number of lives saved," said study co-author David N. Fisman, MD, MPH, FRCP(C) of the Dalla Lana School of Public Health in Toronto, ON, Canada.

According to the authors’ model, clean water distributed to a relatively small subset of the population had a much smaller impact on case counts than vaccination of an identical number of individuals. This is because individuals who are protected from cholera via clean water are still vulnerable to infection through other routes, such as person-to-person transmission. Vaccinated individuals will not contract cholera or pass it along to others.

The authors of an accompanying editorial write that a comprehensive intervention strategy should include oral and intravenous rehydration and antibiotic therapy and cleaning up the public water and sanitation systems in addition to the vaccination program. In addition, surveillance must become part of Haiti’s immediate epidemic response and its ongoing overall health infrastructure. Education, prevention, a secure supply chain, and treatment efforts must be integrated. As prevention and treatment interventions are expanded, evidence regarding their efficacy should guide future implementation strategies. Such mechanisms could strengthen Haiti’s health system and give it the tools to respond to future health crises.

"Our study suggests that the cholera epidemic in Haiti is likely to last well into 2011,” said Dr. Fisman. "We hope that our research may spur the international community to provide the additional logistical, economic, and political support that is needed to quell this epidemic and save lives."

Journal Reference:

Class of Potent Anti-Cancer Compounds Discovered

ScienceDaily (Mar. 7, 2011) — Working as part of a public program to screen compounds to find potential medicines and other biologically useful molecules, scientists from The Scripps Research Institute and Massachusetts Institute of Technology (MIT) have discovered an extremely potent class of potential anti-cancer and anti-neurodegenerative disorder compounds. The scientists hope their findings will one day lead to new therapies for cancer and Alzheimer’s disease patients.

The research—scheduled for publication in the journal Proceedings of the National Academy of Sciences (PNAS) the week of March 7, 2011—was led by Benjamin F. Cravatt III, professor and chair of the Department of Chemical Physiology at Scripps Research and a member of its Skaggs Institute for Chemical Biology, and MIT chemistry professor Gregory Fu.

"It was immediately clear that a single class of compounds stood out," said Daniel Bachovchin, a graduate student in the Cravatt lab and the study’s first author. "The fact that these compounds work so
potently and selectively in cancer cells and mice, right off the screening deck and before we'd done any medicinal chemistry, is very encouraging and also very unusual."

**Browsing in the Public Library**
The National Institutes of Health (NIH) Common Fund Molecular Libraries Program currently funds nine screening and medicinal chemistry-related centers at academic institutions around the United States to enable scientists to find biologically interesting molecules, independently of commercial labs. In these centers, academic scientists can test thousands of compounds at once through high-throughput screens against various biological targets to uncover "proof-of-concept" molecules useful in studying human health and in developing new treatments for human diseases.

"Initially the compounds in the NIH Molecular Libraries repository were purchased from commercial sources and augmented through chemical diversity initiatives," explained Ingrid Y. Li, director of the Molecular Libraries Program at the NIH National Institute of Mental Health (NIMH). "In recent years we've also encouraged academics to donate structurally unusual compounds, to add novelty to the library."

In 2008, Fu's lab donated a set of molecules known as aza-beta-lactams (ABLs)—molecular cousins of penicillin and other beta-lactam antibiotics. "These were molecules that probably didn't exist in commercial compound libraries, and their bioactivity had been virtually unexplored," said Fu.

Meanwhile, across the country, in the Cravatt lab at Scripps Research campus in La Jolla, California, Bachovchin was developing an unusually fast and flexible test for enzyme activity, using fluorescent molecular probes that bind to an enzyme's active site. Researchers can use such tests to measure whether an enzyme of interest loses its activity in the presence of another chemical compound. Bachovchin, Cravatt, and their colleagues decided to apply the new technique to the NIH compound library, to find an inhibitor for an enzyme known as PME-1 (phosphatase methylesterase 1).

"Despite its importance, no one had been able to develop a PME-1 inhibitor, mainly because standard substrate assays for the enzyme were difficult to adapt for high-throughput screening," said Cravatt. "But we believed that we could use our new 'substrate-free' screening technology for PME-1; and we knew that we needed to try a large, high-throughput screen, because our small-scale efforts to find PME-1 inhibitors had come up empty."

Scripps Research runs an NIH Molecular Libraries Program screening center at its Jupiter, Florida campus. There, the institute's researchers set up an automated version of Bachovchin's new screening technique and used it to search for strong PME-1 inhibitors among the 300,000-plus small-molecule compounds in the NIH library.

**Super Potent, Super Selective**
Like many molecules, ABLs can exist in two mirror-image versions, known as enantiomers, and they usually are synthesized as an equal mixture of both compounds. But Fu and his group had used new chemistry techniques to produce the ABLs in an "enantiomerically selective" way, in case one enantiomer of a compound had more activity than its mirror-image twin. And, in fact, one of these enantiomeric molecules, ABL127, turned out to fit so precisely into a nook on PME-1 that it completely blocked PME-1 activity in cell cultures and in the brains of mice. Aside from being extremely potent, it also was highly selective for PME-1, so that even at higher doses, it had negligible effects on other enzymes in the PME-1 family, known as serine hydrolases. In mice, ABL127's inhibition of PME-1 activity caused a more than one-third drop in the measured level of demethylated ("inactive") PP2A.

The Cravatt and Fu labs are now working together to synthesize more ABLs and explore their chemistry, looking for the best possible PME-1 inhibitor. The near-term goal is to use ABL127 as a scientific probe to study PME-1 functions in animals. A longer-term goal is to develop ABL127, or related compounds, as potential oncology or Alzheimer's disease drugs.

"Already several labs from both academia and industry have contacted us about collaborating on PME-1 research," said Cravatt. "So our findings here are scientifically interesting, and I think could, one day, be valuable clinically. But it's important to emphasize that we wouldn't have these findings at all, were it not for the NIH Molecular Libraries Program and its compound library. Both on the screening side and the chemistry side, the NIH enabled us academics to bring technologies to the table unlikely to be
found in a traditional 'pharma' setting. Our discoveries thus stand as a fine example of the value of public screening for creating novel, in vivo-active pharmacological probes for challenging protein targets."

**Journal Reference:**

**New Compound Rids Cells of Alzheimer Protein Debris**

ScienceDaily (Mar. 7, 2011) — If you can’t stop the beta-amyloid protein plaques from forming in Alzheimer’s disease patients, then maybe you can help the body rid itself of them instead. At least that’s what scientists from New York were hoping for when they found a drug candidate to do just that. Their work appears in a research report online in The FASEB Journal, and shows that a new compound, called "SMER28" stimulated autophagy in rat and mice cells.

"Autophagy is a process cells use to "clean out" the debris from their interior, including unwanted materials such as the protein aggregates that are hallmarks of Alzheimer's disease. In mice and rat cells, SMER28 effectively slowed down the accumulation of beta-amyloid.

"Our work demonstrates that small molecules can be developed as therapies, by activating a cellular function called autophagy, to prevent Alzheimer's disease," said Paul Greengard, Ph.D., Nobel laureate and director of the Laboratory of Molecular and Cellular Neuroscience at The Rockefeller University in New York, NY. "By increasing our understanding of autophagy, it might be possible to stimulate it pharmacologically or naturally to improve the quality of life for aging people."

Using mouse and rat cells, scientists tested various compounds for their ability to reduce the buildup of beta-amyloid by exposing cultured cells to compounds known to activate autophagy. The effects of these compounds were then compared by removing growth factors from the culture medium. Researchers then focused on the most effective compound, which was SMER28, to characterize the cellular components involved in this phenomenon. For that purpose, the effect of SMER28 on beta-amyloid formation was compared using normal cells or cells where the expression of genes known to be involved in autophagy was reduced or abolished. Results showed involvement of three important autophagic players, and one was essential for the effect of SMER28. This research represents a radically different approach to treating Alzheimer's disease, namely boosting a cellular mechanism to enhance the clearance of beta-amyloid, as well as other protein aggregates; and it opens a new therapeutic avenue for the treatment of this and other degenerative diseases.

"Autophagy has been called the cell's equivalent of urban renewal. In that sense, SMER28 functions as a cellular forklift to clear out unwanted debris," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. "The Rockefeller group shows that small molecules can be developed as therapies, by activating a cellular function called autophagy, to prevent Alzheimer's disease,“ said Fidel Ngabo, the health ministry's director of nursing, mother and child health. “In the past, the more children a farmer had, the more wealth he had. But that has radically changed. Now more children mean more education and health care costs for the agricultural worker as well as less land for each child to inherit.”

Ngabo said NSV services will be bundled along with complimentary HIV risk reduction and family planning counseling. “We always give HIV and family planning counseling together because they go hand in hand,” Ngabo said. “With vasectomies, we give this counseling both before and after the procedure.”

Developed in China during the late 1970s, NSVs are quicker, cheaper, and less complicated than female sterilization, officials said.

“The procedure takes about 15 minutes and is painless,” said Leonard Kagabo, the program trainer. “We use only a very small needle along with a local anesthetic.”

**Rwanda Looks to Vasectomy to Tackle Population Growth**

Agence France Presse, (03.06.2011)
The most densely populated nation in the African mainland is adding no-scalpel vasectomies to its expanding family planning services. Over the past 50 years, Rwanda’s population has risen four-fold and now tops 10 million. The tiny nation’s government ranks overpopulation as a chief threat to development. Some experts, however, worry that NSVs will lead to lower condom use rates and fuel HIV's spread.

“Eighty percent of our population lives off the land,” said Fidel Ngabo, the health ministry’s director of nursing, mother and child health. “In the past, the more children a farmer had, the more wealth he had. But that has radically changed. Now more children mean more education and health care costs for the agricultural worker as well as less land for each child to inherit.”

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Malaria’s Weakest Link: Class of Chemotherapy Drugs Also Kills the Parasite That Causes Malaria

ScienceDaily (Mar. 8, 2011) — A group of researchers from EPFL’s Global Health Institute (GHI) and Inserm (Institut National de la Santé et de la Recherche Médicale, the French government agency for biomedical research) has discovered that a class of chemotherapy drugs originally designed to inhibit key signaling pathways in cancer cells also kills the parasite that causes malaria. The discovery could quickly open up a whole new strategy for combating this deadly disease.

The research, published online in the journal Cellular Microbiology, shows that the malaria parasite depends upon a signaling pathway present in the host—initially in liver cells, and then in red blood cells—in order to proliferate. The enzymes active in the signaling pathway are not encoded by the parasite, but rather hijacked by the parasite to serve its own purposes. These same pathways are targeted by a new class of molecules developed for cancer chemotherapy known as kinase inhibitors. When the GHI/Inserm team treated red blood cells infected with malaria with the chemotherapy drug, the parasite was stopped in its tracks.

Professor Christian Doerig and his colleagues tested red blood cells infected with Plasmodium falciparum parasites and showed that the specific PAK-MEK signaling pathway was more highly activated in infected cells than in uninfected cells. When they disabled the pathway pharmacologically, the parasite was unable to proliferate and died. Applied in vitro, the chemotherapy drug also killed a rodent version of malaria (P. berghei), in both liver cells and red blood cells. This indicates that hijacking the host cell’s signaling pathway is a generalized strategy used by malaria, and thus disabling that pathway would likely be an effective strategy in combating the many strains of the parasite known to infect humans.

Malaria infects 250 million and kills 1-3 million people every year worldwide. Efforts to find a treatment have been marred by the propensity of the parasite to quickly develop drug resistance through selection of mutations. Once in the body, it hides from the immune system inside liver and blood cells, where it proliferates. The discovery that the parasite hijacks a signaling pathway in the host cell opens up a whole new strategy for fighting the disease. Instead of targeting the parasite itself, we could make the host cell environment useless to it, thus putting an end to the deadly cycle. Because this strategy uniquely targets host cell enzymes, the parasite will be deprived of a major modus operandi for development of drug resistance—selection of mutations in the drug target.

Several kinase-inhibiting chemotherapy drugs are already used clinically, and many more have passed stage 1 and stage 2 clinical trials. Even though these drugs have toxic effects, they are still being used or considered for use over extended periods for cancer treatment. Using them to combat malaria would involve a much shorter treatment period, making the problem of toxicity less acute. The authors of the study suggest evaluating these drugs for antimalarial properties, thus drastically reducing the time and cost required to put this new malaria-fighting strategy into practice.

Journal Reference:

At least one in six patients maintains a viral load over one hundred thousand

Gus Cairns
Published: 09 March 2011

A study of patients in southern Africa diagnosed during primary HIV infection has found that one in five maintained viral loads over 100,000 copies/ml for at least 400 days after infection. One in six will maintain such a persistent high viral load for three years or more, researchers calculated.

Quantifying the percentage of patients who, off treatment, maintain high viral loads is important for calculating the likely transmission rate within a population and the prevention impact of treating them. Another study presented at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) last week found that an individual with a viral load of 100,000 copies/ml is likely to transmit HIV nearly three times more often than a person with a viral load of 10,000 copies/ml.

The southern African study, from Vladimir Novitsky and colleagues from Harvard Medical School, also found that patients with viral loads over 100,000 copies/ml experienced dramatically faster declines in their CD4 counts.
The study looked at 75 patients from Durban in South Africa and Gaborone in Botswana who were diagnosed while they had acute HIV infection (defined as within 30 days of the estimated date of infection). These 75 patients were followed for an average time of 573 days and had an average of four viral load tests during that time.

The researchers found that one-third of the patients maintained a viral load over 100,000 copies/ml between 100 and 300 days after infection, and 16% between 200 and 400 days after infection. Extrapolating the viral decay curve led to an estimate that 16% of patients would maintain such a consistently high viral load for at least 900 days post-infection. Three people (3.4%) maintained a viral load of over one million between days 100 and 300 post-infection.

Patients with viral loads over 100,000 experienced dramatically faster falls in their CD4 count. Their CD4 counts had fallen to below 350 cells/mm$^3$, the threshold at which the World Health Organization recommends treatment, less than three months after infection compared with nearly two years for other patients, and to 200 cells/mm$^3$ one year after infection, compared with three years for other patients.

This is not the first study either to quantify the proportion of patients with high viral loads or to find that their CD4 counts declined faster. Another study from New York (Laraque) found that 7% of patients in New York had at least two consecutive viral loads over 100,000 copies/ml between 2007 and 2009, in a population where 53% had undetectable viral loads.

But this is one of the first longitudinal viral load studies from southern Africa, where a single subtype of HIV, subtype C, predominates. "People [with] extended high viremia....may fuel the AIDS epidemic," comment the researchers.

### References


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**Russia discriminates against man with HIV—court**

Agence France-Presse
First Posted 02:07:00 03/11/2011

STRASBOURG—Russia discriminated against an Uzbek man by refusing him permission to stay in the country because he was HIV-positive, the European Court of Human Rights said on Thursday.

Viktor Kiyutin, who was awarded 15,000 euros (20,000 dollars) in damages, married a Russian woman but his request for a residence permit was refused in line with Russian law.

The court acknowledged that the man did not have the right to settle in any country of his choice under the European Convention on Human Rights, but said that people with HIV were a "vulnerable group in society".

Any government, it said, should therefore have very strong reasons for imposing restrictions.

"Just the presence of an HIV positive person in the country does not in itself constitute a threat to public health," the Strasbourg judges said.

The court ruled that Kiyutin was a victim of discrimination based on his health.

Of the 47 countries that are signatories to the European Convention on Human Rights only Moldova, Armenia and Russia expel foreigners on grounds of their HIV status.

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**Taiwan scientists document first case of knife-wound HIV infection**

Publication Date : 03/11/2011

The world’s first case of HIV transmission via a knife wound has now been scientifically established, scientists from Taiwan reported March 10.

The researchers said their findings have been published by the AIDS Research and Human Retrovirus Journal, one of the world’s leading journals on AIDS research.

The case stems from a violent encounter in 2008 between a man in his 70s and a 42-year-old hoodlum, who demanded money from the elderly citizen. When the man refused to comply, he was attacked with a watermelon knife.

Although the old man fought back valiantly with his cane to resist the criminal’s ferocious assault, he ended up in a pool of his own blood. Blood from the hoodlum, who was also wounded during the attack, gained entry into the old man as a result of his open wounds.
The old man was hospitalized for three months. Six months after the attack had occurred, he was informed that he had become a carrier of HIV.

The Centers for Disease Control subsequently got involved in investigating the HIV transmission case. After ruling out a sex or a blood transfusion-related transmission, the CDC determined, via gene sequencing technology, including advanced molecular biology cross matching and HIV antibody concentration analysis, that he had contracted HIV from his assailant.

When the investigation was concluded, the CDC, along with research teams from National Yang Ming University and National Taiwan University, submitted a report of the case to AIDS Research and Human Retrovirus Journal.

Researchers from the CDC confirmed that this was the first article to be published internationally showing that antibody concentration analysis and molecular biology tests could be used to confirm the path of AIDS infection.

The report stated the most common paths for passing the virus to another person are sexual activity, followed by the sharing of needles and blood transfusions.

A few sporadic cases of HIV transmission through deep kissing or fist fights have also been documented. But chances of contracting HIV through these means or by knife wounds are miniscule, the CDC stressed.

Record Numbers of New Zealand Gay, Bisexual Men Diagnosed with HIV

*New Zealand Herald*, (03.07.2011) Hayden Donnell

Last year 149 people were newly diagnosed with HIV in New Zealand, including 90 gay and bisexual men, according to data from the AIDS Epidemiology Group at the University of Otago.

The mode of infection is still unknown for 23 cases. However, if just a few of these cases are men who have sex with men, 2010 would set a record high for HIV cases among MSM — up from 93 in 2008. In contrast, the 35 heterosexually acquired cases last year represent a record low.

An AIDS diagnosis was made for 39 people last year, including 25 infected homosexually, 11 heterosexually, one by injection drug use, and two by unknown means.

The situation has never been worse for New Zealand's gay community, said Shaun Robinson, director of New Zealand AIDS Foundation. “Not even in the early days of AIDS in the 1980s were rates of infection this bad in New Zealand,” he said, estimating about 15 of the unknown-cause cases to be MSM.

“These men may have had HIV and been sexually active for a long time before they were diagnosed, which means they missed out on treatment and were also likely to be more infectious,” Robinson said. “This situation could have been avoided by regular testing.”

Robinson urged MSM to use condoms and test regularly: “We will be increasing our efforts to make this a widespread community norm.”

Help on Horseback for AIDS Sufferers in Mountain Kingdom

*CNN.com*, (02.04.2011) Robyn Curnow

The African kingdom of Lesotho has myriad exceptional traits. It is a sovereign nation landlocked by South Africa; 80 percent of the kingdom lies above 1,800 meters; and one-third of its 2 million people live in remote communities cut off for months at a time due to inclement weather. Worse still, more than one-quarter of its residents have HIV/AIDS.

In order to bring antiretroviral medication to those living with HIV/AIDS in isolated areas, Dr. Leo Buhendwa, modified the traditional practice of using horses for transportation and established the Horse Riding for Health (HRH) program. The program benefits from its riders’ intimate familiarity with the terrain.

“Thirty percent of the population was cut off for four months” because of torrential rains and snow accumulation, said Buhendwa, country director for the Elizabeth Glaser Pediatric AIDS Foundation. “For months they couldn’t access care; they couldn’t access treatment; and they couldn’t access prevention services. So we had to find a solution.”

Since horses are the sole means of winter transportation in the mountains, HRH uses them to service far-flung clinics situated in steep, unforgiving territory. One clinic is so remote its staff nurse boards there, as trekking back and forth to work would be too grueling.

That rural clinic assists 152 HIV patients and is now helped by HRH, which has four horse riders servicing its region. One rider, Potso, makes the same 30-minute journey numerous times each week between a Red Cross clinic and the secluded treatment center.
“If my brother was aware of HIV and AIDS and the drugs that were available, he wouldn’t be dead,” said Potso. “I wanted to be a horse rider because I wanted to help the people. I didn’t want to be in that disaster again.”

Antiretroviral Therapy and Sexual Behavior in Uganda: A Cohort Study

AIDS Vol. 25; No. 5: P. 671-678, (03.13.2011) Leigh Anne Shafer; Rebecca Nsubuga; Richard White; Billy N. Mayanja; Ruth Chapman; Katie O’Brien; Lieve van der Paal; Heiner Grosskurth; Dermot Maher

The current study examined evidence for sexual behavior change in response to antiretroviral therapy (ART) among participants of a clinical cohort in Uganda. In addition, the investigators assessed factors associated with both sexual behavior and ART independently, with the goal of understanding the impact ART is likely to have on the epidemic.

A retrospective analysis was conducted on an open cohort where ART roll-out began in 2004. Three-month data from 2002 to 2009 were used to examine associations between ART initiation timing and sexual behavior among HIV-infected participants, and timing of ART availability and sexual behavior among uninfected participants. Partner turnover rates and the proportion of HIV-infected participants on ART, two key factors for modeling the potential impact of ART on the epidemic, were also studied.

Though risky sexual behavior among HIV-infected people rose on several indicators following ART initiation, it was not seen at levels higher than two or more years before initiation. “Some evidence suggests that the availability of ART may impact risky behavior among HIV-uninfected people, although this was inconsistent across different reported behavior variables,” according to the results.

“The HIV-uninfected is larger than the HIV-infected population. If risky behavior among this population increases due to the feeling of safety that ART provides, this will affect the impact of ART on the HIV epidemic,” the investigators concluded. “Policy makers are urged to intensify messages associating sexual behavior and HIV and to target both HIV-infected and –uninfected people.”

Research suggests HIV-infected patients at higher risk for bone fractures

Study compared fracture rates among HIV patients with general US population

[EMBARGOED FOR MARCH 11, 2011] Low bone mineral density in HIV-infected patients is common and raises concerns about increased risks of fracture. Although there have been several studies regarding bone mineral density, there have been few data on rates of fracture in this population. A new study published in Clinical Infectious Diseases and available online (http://www.oxfordjournals.org/our_journals/cid/ciq242.pdf) examined differences in the rates of bone fractures between HIV-infected patients and the general population and found higher rates of fracture among HIV patients.

A total of 5,826 HIV-infected patients were analyzed from 2000 to 2008 in the study. The researchers were able to compare rates with persons in the general U.S. population for the period from 2000 to 2006 and observed that annual fracture rates among HIV-infected patients were between 1.98 and 3.69 times greater.

"We confirmed that several established risk factors for fracture, such as age, substance abuse, hepatitis C co-infection, and diabetes, were associated with fractures among the HIV-infected patients," said study author Benjamin Young, MD, PhD, of the Rocky Mountain Center for AIDS Research, Education, and Services in Denver. "This study also highlights for the first time a potential association between fracture risk and CD4 cell count. The optimal clinical management of bone health in HIV-infected individuals is not well defined and remains controversial."

Dr. Young added, "We believe our data support the need to develop guidelines that address screening for and correcting reversible causes of low bone mineral density and fall risk and that these activities should be incorporated into the routine care of HIV-infected patients."


Missing DNA Helps Make Us Human

ScienceDaily (Mar. 9, 2011) — A new study demonstrates that specific traits that distinguish humans from their closest living relatives—chimpanzees, with whom we share 96 percent of our DNA—can be attributed to the loss of chunks of DNA that control when and where certain genes are turned on. The finding mirrors accumulating evidence from other species that changes to regulatory regions of DNA—rather than to the genes themselves—underlie many of the new features that organisms acquire through evolution.
Seeking specific genetic changes that might be responsible for the evolution of uniquely human traits, Howard Hughes Medical Institute investigator David Kingsley and colleagues at Stanford University scanned the human genome for features that set us apart from other mammals. The team found 510 segments that are present in chimps and other animals but missing from the human genome. Only one of the missing segments would actually disrupt a gene; the remaining 509 affect the DNA that surrounds genes, where regulatory sequences lie.

Careful analysis of a handful of these segments demonstrated that loss of regulatory DNA could explain how humans developed some features not found in other animals—such as big brains—as well as how they lost features common in other species, such as sensory whiskers and spiny penises. Their findings are published in the March 10, 2011, issue of the journal Nature.

Genes—segments of DNA that carry the blueprints for proteins—make up less than two percent of the human genome. Hidden within the remainder of our more than three billion base pairs of DNA are regulatory sequences that control when and where genes are expressed. Direct alterations to a gene can have dramatic effects, sometimes killing an organism or rendering it sterile. "In contrast, if you alter the way [a gene] turns on or off at a particular place in development, that can have a very large effect on a particular structure, but still preserve the other functions of the gene," Kingsley says. "That tends to be the sort of alternation that's favored when a new trait is evolving."

Kingsley’s previous work with stickleback fish, a small spiny fish whose recent and rapid adaptation to a wide range of aquatic environments has made it ideal for evolutionary studies, have shown time and again that changes in regulatory DNA can have profound effects on an organism’s traits. So when Kingsley and his colleagues searched for regions of the genome common to chimps, macaques, and mice but missing in the human genome, they weren't surprised that the sequence differences they found were almost exclusively outside of genes.

Collaborating with computational biologist Gill Bejerano’s lab at Stanford, the team pinpointed 510 genetic sequences that appear in the genomes of chimps and other animals, but are "surprisingly missing" from the human genome, Kingsley says. To narrow the list so that they could focus on the changes most likely to have altered when and where particular genes were expressed, the researchers conducted a computer analysis to identify deletions that were clustered around particular genes. "We saw more changes than you would expect near genes involved in steroid hormone signaling," Kingsley says. A number of deletions also appeared near genes involved in neural development, their analysis revealed.

But technology could only take the team so far. To zero in on specific deletions that might control human traits, the team relied on manpower: neuroscientists, physical anthropologists, developmental geneticists, and more. "We had a team of interested graduate students, postdocs, and developmental biologists poring through this list," Kingsley says. The team searched for sequences near genes known to play key roles in development, especially those known to control traits that differ between humans and other animals. "It was a fun detective hunt that led to lots of interesting discussions," he says.

The team came up with a couple dozen deletions near genes they suspected might be involved in the evolution of particular human traits. But the researchers still didn’t know the normal functional roles of the missing sequences. So Kingsley and his colleagues isolated those genetic sequences from organisms that still had them (chimps or mice), attached the sequences to a reporter gene that produces a simple blue color reaction in living cells, and injected the resulting sequences into fertilized mouse eggs. By monitoring the blue color reaction in developing mice, they could see exactly where and when the sequence was turning on gene expression during embryonic or postnatal development. This gave them a way to link "the biology of the gene, the molecular change that had happened in humans, and the specific anatomical place where it really was expressed during normal development," Kingsley explains.

These experiments highlighted two segments of DNA that humans lack, but that appear to play a particularly important role in development of mice and other non-human mammals. The first is a segment of DNA that, in most animals, occurs near the gene that codes for the androgen receptor, which is associated with a variety of male-specific traits. "Males have beards, females don’t," Kingsley says. "That’s an example of an androgen receptor-dependent process." When the researchers inserted this sequence into mouse eggs, "what we got were blue sensory whiskers and blue genitalia," Kingsley says, indicating that when present, the sequence causes the androgen receptor to be produced in those regions.

Tracing the expression of the protein through development, Kingsley and his colleagues concluded that the sequence contributes to the development of sensory whiskers found on the faces of many mammals, and prickly surface spines found on the penises of mice and many non-human primates. Previous studies show that complete inactivation of the androgen receptor gene lead to defects in whiskers and failure to form penile spines. Although humans still retain the androgen receptor gene, the
loss of regulatory information for expression in whiskers and spines could help explain two human-specific anatomical traits: absence of sensory whiskers and lack of spines on human penises. Loss of penile spines is one of several traits thought to be related to evolution of pair-bonding and monogamy in the human lineage.

The second segment of regulatory DNA they tested appears, in non-humans, near a gene called GADD45g. GADD45g normally represses cell growth. In fact, Kingsley said, "if the gene is missing entirely, unchecked cell growth can cause pituitary tumors." When they injected the sequence into mouse eggs, they found the tell-tale blue color in a key growth layer of the developing brain—indicating that in most animals, the regulatory sequence that has disappeared in humans restricts brain growth.

The study describes some of the changes that have helped make humans human, but there are likely to be many more, Kingsley says. "By simply changing a single gene like GADD45g you're not going to be able to explain all of human brain evolution."

Still, he adds, the study shows that "it's now possible to begin identifying some of the particular molecular changes that contribute to the evolution of human traits." Human-specific traits include not only anatomical and physiological differences, but also differences in our susceptibility to many diseases, such as arthritis, cancer, malaria, HIV, Alzheimer's, and Parkinson's. "We think that the same sorts of lists and approaches will eventually help illuminate human disease susceptibilities as well," he says. "It's a great time to be studying not only where we came from, but also how our genetic history shapes many aspects of current human biology."

**Journal Reference:**

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**Function of 'Junk DNA' in Human Genes**
ScienceDaily (Mar. 8, 2011) — Part of the answer to how and why primates differ from other mammals, and humans differ from other primates, may lie in the repetitive stretches of the genome that were once considered "junk."

A new study by researchers at the University of Iowa Carver College of Medicine finds that when a particular type of repetitive DNA segment, known as an Alu element, is inserted into existing genes, they can alter the rate at which proteins are produced—a mechanism that could contribute to the evolution of different biological characteristics in different species. The study was published in the Feb. 15 issue of the journal Proceedings of the National Academy of Sciences (PNAS).

"Repetitive elements of the genome can provide a playground for the creation of new evolutionary characteristics," Xing said. "By understanding how these elements function, we can learn more about genetic mechanisms that might contribute to uniquely human traits."

Alu elements are a specific class of repetitive DNA that first appeared about 60 to 70 million years ago during primate evolution. They do not exist in genomes of other mammals. Alu elements are the most common form of mobile DNA in the human genome, and are able to transpose, or jump, to different positions in the genome sequence. When they jump into regions of the genome containing existing genes, these elements can become new exons—pieces of messenger RNAs that carry the genetic information.

Although scientists have known for more than a decade that these Alu elements are an important source of new exons in the human genome, it has been more difficult to determine if these new exons are biologically important.

"It's been hard to say whether these Alu-derived exons actually do anything on a genome-wide level," said senior study author Yi Xing, Ph.D., assistant professor of internal medicine and biomedical engineering, who holds a joint appointment in the UI Carver College of Medicine and the UI College of Engineering. "Our new study says they do—they affect protein production by altering the efficiency with which messenger RNA is translated into protein."

Xing noted that in other circumstances, altering the rate of protein production can cause disease, meaning that a mechanism that can affect protein production can have a real impact on the characteristics of an organism.

"This would not be the only mechanism that might differentiate humans from other primates, but our study suggests that the creation of new exons from Alu elements is an important process that contributes to those differences," Xing said.

The UI team, including co-first authors Shihao Shen, doctoral student in the Department of Biostatistics; and Lan Lin, Ph.D., associate in the Department of Internal Medicine, made use of data from
a new technology called high throughput RNA sequencing to analyze more than 120 million RNA sequences from human cerebellum. Using this data, the team was able to quantify how often Alu-derived exons were included in the mature RNA sequences, which provide the final blueprint for protein production, and where they were inserted in the genes.

"What we found is that these exons tend to avoid protein-coding regions of the genes and rather they end up in the non-coding region that precedes the protein-coding region, called the five prime untranslated region or 5' UTR," Xing explained. "This is the part of the gene that usually contains regions that help control the stability of the messenger RNA and the efficiency at which the messenger RNA is translated into protein."

Experiments to probe the function of these newly inserted elements proved that Alu exons in this region are able to alter the efficiency of messenger RNA translation, which means they affect how fast protein is produced from the altered genes.

The study also suggests that the effect of the newly created exons might be amplified because of which genes were "targeted" by the Alu exons. The researchers found that Alu exons are highly enriched in genes that code for zinc-finger transcription factors—proteins that act as master regulators of gene expression and that previously have been linked to human and primate evolution. Because these transcription factors control the expression of thousands of other genes, any changes to the amount of transcription factor available would likely have a cascade effect on the downstream genes.

In addition to Xing, Shen and Lin, the team included UI researchers Peng Jiang, Ph.D.; Elizabeth Kenkel; Mallory Stroik; Seiko Sato; and Beverly Davidson, Ph.D., professor of internal medicine, neurology and molecular physiology and biophysics. The team also included James Cai, Ph.D., assistant professor of veterinary medicine at Texas A&M University.

**Journal Reference:**

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**Gaddafi’s HIV Shakedown**

By falsely accusing a Palestinian doctor and five Bulgarian nurses of infecting hundreds of children, Libya managed to blackmail its way to hundreds of millions of dollars’ worth of aid.

Zakia Saltani has been warned not to talk to the press. She doesn’t care. She has waited 13 years to tell her story, and the Libyan government’s threats can’t stop her now. “After what happened to my family, what more can they do?” she asks. “I am beyond fear.”

At her friend’s house in Benghazi, with the red-black-and-green flag of the anti-Gaddafi rebellion spread proudly across her shoulders, she shows a framed photograph of her son, Ashur. He died of AIDS-related complications in May 2005, when he was 8. He had been one of more than 400 Libyan children who were admitted to the Al Fateh pediatric hospital in Benghazi 13 years ago with routine complaints like colds and earaches. They left with HIV. Like Ashur, roughly 60 have since died. Others are hanging on.

Until the Feb. 20 liberation of Benghazi by anti-Gaddafi protesters, the regime was able to bully people like Saltani into silence. Meanwhile, the government blamed the outbreak on five Bulgarian nurses and a Palestinian doctor at the hospital, falsely accusing them of deliberately infecting their young patients, and sentencing them to death. The medics were finally released in 2007, but not before the regime had extorted an Eastern European debt-forgiveness package and roughly three quarters of a billion dollars in supposed compensation and health-care assistance, together with a civilian nuclear-development deal and a “very good military accord” (in the words of Gaddafi’s British-educated son Saif al-Islam) with the French government “and other confidential stuff we shouldn’t discuss on the record,” the smiling Saif told NEWSWEEK at the time.

Now Saltani and other ordinary Libyans are starting to speak out at last. She says this is the first interview she has ever given—and her anger against Muammar Gaddafi and his 41-year dictatorship begins to spill out. “On Feb. 2, 1998, we went to the hospital because Ashur had a fever and a cough,” she says. “He was 4 months old, and we stayed two days. We went back two weeks later for the same problems.” Shortly afterward she took her 5-year-old daughter, Mouna, to the same hospital with a high fever. Mouna also went home with HIV, although at the time Saltani had no way of knowing that either child had become infected.
The truth began to emerge a few months later. “In October we learned that the doctors were hiding something,” Saltani recalls. “They said there was something in his blood that they couldn’t identify. The head of the hospital told us not to say anything. When we found out it was HIV, the government told us the infection originated from outside Libya, and that it only affected 10 kids. Another doctor even tried to convince us that it wasn’t HIV, but tuberculosis.” When the families finally discovered just how many children had been infected, the regime sent many of the patients to Italy for analysis and treatment.

 Foreign medics made useful scapegoats—and lucrative hostages.

 Even then the regime still did its best to cover up the outbreak. Mohammed El Agili, 20, says he was 8 when his parents took him to Al Fateh for an eye operation in March 1998. Three days later he returned, still dizzy from the procedure. When rumors of AIDS swept through the city, he underwent HIV testing, along with all the other children who had been admitted to the hospital in early 1998. The result came back positive. “When I found out, I ran shouting through the streets like a lunatic,” says his father, Mahmoud. “And we made sure the government heard our cries. Gaddafi invited all the families to a tent in the desert outside Sert, saying he would give us whatever we wanted, but we had to keep quiet. ‘We don’t want foreigners to become involved in this,’ Gaddafi told us. ‘We don’t want this to get out of Libya.’ He warned us that our relatives outside Libya would be in danger if we talked. We were afraid. We had to keep quiet.”

 The news blackout may have suited Gaddafi’s purposes, but it didn’t help young Mohammed deal with insensitive classmates. They bullied him until he finally gave up school at 12. A rabid fan of the Real Madrid football team, he now helps his brother run a mobile-phone shop near their house. Asked about his future, the HIV patient smiles at the question’s naiveté. “My generation doesn’t think about the future,” he says. “Even without this disease, Gaddafi has destroyed all our futures.”

 Although the cause of the outbreak remains a mystery, outside studies implicate poor hygiene at the hospital rather than any of the conspiracy theories that abound in Libya. According to a 2002 report by Italian medical investigators, all the infected children had received intravenous fluids, antibiotics, steroids, or bronchodilators, but no blood or blood products. Saltani says she found it hard to accept the regime’s allegations against the hospital’s foreign medical workers. “At first I didn’t believe it was them,” she says. “The Palestinian doctor and the Bulgarians had always taken good care of the children, but everyone was blaming them, so we believed it. We wanted to confront them face to face, but the government wouldn’t let us.”

 Still, the foreign medics made useful scapegoats—and lucrative hostages. The ransom Gaddafi received for freeing them enabled him to pay the victims’ families roughly $1 million each, helping him to buy a little more silence. For 41 years he has controlled the country through a combination of violence, intimidation, and strategic payoffs. To test the regime’s limits on free speech was to risk imprisonment, torture, and death. And old habits persist, even in liberated Benghazi, where anti-Gaddafi rallies occur daily. The current director of Al Fateh Hospital, who was working there as a doctor when the infections took place, refuses to speak as long as Gaddafi holds sway in Tripoli.

 Just before Saltani’s interview, her phone rings. The caller is Ibrahim El Oraibi, the representative who deals with the regime on behalf of the HIV families. She puts it on speakerphone so a reporter can hear. He screams at Saltani for violating the government’s gag order. “If Tripoli finds out, they will get angry and will stop sending AIDS medication to Benghazi!” Oraibi shouts. That could be a death sentence for Saltani: she herself contracted HIV from breast-feeding Ashur. Doctors say it’s a thing that happens only rarely, but it can happen. She has been taking antiretroviral drugs for a year, and has only two months’ supply left.

 But she refuses to back down. “I don’t believe anything Gaddafi says anymore,” Saltani tells Oraibi. “I have been quiet for 13 years and I’m tired of it. I want to fight.” The intermediary pleads: “Don’t talk until we receive the medicine.” Saltani is unmoved. “Gaddafi needs to go—and you can go with him,” she says. “I’ve been waiting 13 years and I’m not going to wait any longer. He’s a liar, and I’m going to talk with whomever I wish.”

 She hangs up on the caller and begins her interview.

**Gilead’s High Bar for AIDS Drugs Means New Development Withers**

Sunday, March 13, 2011

March 14 (Bloomberg)—Gilead Sciences Inc., the world's biggest AIDS-drug maker, revolutionized treatment and helped forge a $15 billion market with a single daily pill attacking the virus with three medicines at once.
Now, Foster City, California-based Gilead and rivals Merck & Co. and Bristol-Myers Squibb Co. are victims of that success. Three decades after the discovery of the virus that causes AIDS, there are 31 drugs on the market that have helped turn HIV from a death sentence into a manageable disease in the developed world. Only six were approved after 2004.

"The bar for bringing on a drug in HIV has gotten higher," said George Hanna, vice president of virology for U.S. medical and HIV early development at Bristol-Myers, based in New York. "You can no longer bring to market a drug you're going to have to take three times a day. All of a sudden, we're seeing a lot less in the pipeline."

Medicines created over the years have become safer, more effective, have attacked the virus in new ways and have eliminated the need for as many as 20 pills a day. As drugmakers struggle to top that achievement, millions of HIV patients face the possibility of the virus becoming fatal again if it shifts shape inside cells to outsmart existing therapies.

HIV has been a formidable foe for drug designers, mutating around chemical hurdles placed in its way. The attack begins when the virus attaches to a cell surface receptor and uses a protein to force its way inside. Most existing families of drugs stop HIV from hijacking proteins to enter cells or block its ability to copy itself once inside.

**Developing Resistance**

Without a steady stream of new medicines to attack the virus in different ways, drug resistance will develop, leaving more patients without a viable treatment, said Scott Hammer, a professor of medicine at Columbia University in New York.

"If we are complacent, resistance will start to spread against the key components of our therapies," Hammer said in an interview. "We need to be ready for that because we won't be able to catch up after it happens."

Gilead generated $6.3 billion from HIV drugs in 2010, capturing more than 40 percent of the market. Atripla, a three-drug combination pill approved in 2006, is the most widely used AIDS medicine. It mixes Gilead's two-drug medicine Truvada, approved in 2004, with Bristol-Myers's pill Sustiva.

Pfizer Inc. and Merck were the last to introduce new families of medicine for HIV in 2007. Selzentry, the first AIDS drug to block the CCR5 pathway that allows cell entry, generated $128 million last year for New York-based Pfizer and its partner GlaxoSmithKline Plc. Merck, based in Whitehouse Station, New Jersey, had 2010 sales of $1.1 billion for Isentress, which inhibits the integrase protein used by HIV to enter healthy immune cells.

**Shrinking Pipelines**

Intenale, from New Brunswick, New Jersey-based Johnson & Johnson, was the last AIDS drug approved—three years ago.

At that time, there were seven drugs in the third and final stage of testing needed for U.S. regulatory approval, according to a report by Treatment Access Group, an AIDS activist and research organization. None have made it to the market, and only two of them remain in third-stage testing.

There are about 60 drugs in various stages of development for HIV, down from 100 in 2006, said Courtney Stanton, an analyst in the infectious diseases group at Decision Resources in Burlington, Massachusetts. Ten were discontinued or put on hold in the past year, while seven now are at the end of development, she said.

Recent failures by Merck and Avex Ltd., an Australian biotechnology company highlight the difficulty drugmakers face in coming up with a medicine that advances HIV treatment.

**Drugs Abandoned**

Merck ended work on vicriviroc, a drug similar to Selzentry, in previously treated patients in January 2010 after it failed to outperform existing therapies. Avexa, an Australian biotechnology company, scrapped apricitabine last May after five years of development. The drug was taken twice daily, putting it at a disadvantage to Gilead's Truvada, one of the best-selling HIV treatments.

The availability of powerful combination treatments in the developed world means the number of people desperate for new drugs and available to participate in studies has plummeted, Decision Resources' Stanton said.

"There are very few HIV patients now who can't find effective treatment," she said in a telephone interview. "And it's become extraordinarily hard to show you are effective in a treatment-experienced HIV patient."

The development process was more productive around the turn of the century. HIV was evading existing treatments, like London-based Glaxo's AZT and Merck's Crixivan, and drug-resistance was spreading. Doctors and patients clamored for additional options, and clinical trials were in demand as the
only way to get the newest treatments. A better understanding of the virus gave drugmakers numerous targets.

**Longer Studies**

Drug studies are also taking more time to complete, said Norbert Bischofberger, Gilead's chief scientific officer. The FDA now wants 48 weeks of data, and will ask companies to keep patients in the study for longer, up from 16 weeks initially, he said. Doctors want to see two or three years of data before putting their patients on a drug. European regulators have proposed extending the studies further to 96 weeks, he said.

"Honestly, that's probably a good thing," Bischofberger said. "It reflects that we have really good regimens."

Gilead is fashioning a new mixture dubbed B-tripla that replaces Bristol's Sustiva in Atripla with Johnson & Johnson's drug TMC278. It also has a four-drug cocktail in development called Quad that uses all Gilead products. Longer term, Gilead is examining ways they could deliver HIV drugs once a month or even less frequently, as with some contraceptives, he said.

**33 Million People**

The number of people with HIV continues to grow. Each year, 56,000 Americans are infected with the virus, particularly gay men and minorities, according to the Centers for Disease Control and Prevention. There were 2.6 million new infections globally in 2009, with more than 33 million people living with the virus, according to UNAIDS. Now, the ultimate goal is a cure.

"The profit motives that drove HIV drug development are no longer there because the drugs are so good," said Jacob Lalezari, director of Quest Clinical Research, a San Francisco clinical trial center, said in an interview. "It's the greatest success of western medicine in our lifetime. And the success of HIV drugs is leading to its own demise."

**An inside look at how the elite control HIV**

In the years since the AIDS epidemic began, it has become clear that there is substantial variation in the way that individuals respond to HIV infection. Although most progress quickly from initial infection to immunodeficiency, a small subset survive for long periods without developing symptoms. These patients, dubbed elite controllers, display undetectable levels of viral replication, but the mechanism that explains how their immune systems effectively control the virus is not understood.

In this paper, Mathias Lichterfeld and colleagues, at Massachusetts General Hospital in Boston, describe that the T cells from elite controllers are relatively resistant to infection with HIV because they upregulate a protein called p21, which in turn inhibits an enzyme required for the virus to replicate. In addition, blocking p21 increased the expression of viral genes. The researchers hope that this finding may inform the design and development of treatment strategies for patients who are more susceptible to the virus' tragic effects.

**Study helps explain how pathogenic E. coli bacterium causes illness**

Scientists at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, have shown how the O157:H7 strain of *Escherichia coli* causes infection and thrives by manipulating the host immune response. The bacterium secretes a protein called NleH1 that directs the host immune enzyme IKK-beta to alter specific immune responses. This process not only helps the bacterium evade elimination by the immune system, it also works to prolong the survival of the infected host, enabling the bacterium to persist and ultimately spread to unaffected individuals. This finely balanced mechanism, observed in both laboratory and animal models, could be relevant to other pathogens involved in foodborne diseases.

While most *E. coli* strains help check the growth of harmful bacteria in the guts of animals and humans, a few *E. coli* strains, such as O157:H7, can cause severe diarrhea, abdominal cramps and, in rare cases, death. Human cases of *E. coli* O157:H7 have been linked to consumption of raw, undercooked, or spoiled meat.

NIAID researchers plan to use the new information to further study how the host immune system mounts a response to *E. coli* O157:H7 when infection begins and how the bacterium selectively blocks these defenses. Several foodborne pathogens, including *Shigella* and *Salmonella*, use a similar secretion system to disrupt host immune responses and infect gut cells.

**ARTICLE:** F. Wan, et al. IKK-beta phosphorylation regulates RPS3 nuclear translocation and NF-kappa B function during infection with *Escherichia coli* strain O157:H7. *Nature Immunology.* DOI 10.1038/ni.2007
Early success of anti-HIV preventive oral drug regimen is promising, but questions remain

New Rochelle, NY, March 14, 2011—The first human studies of an oral drug regimen to prevent HIV infection in high-risk individuals yielded a promising near 50% reduction in HIV incidence, but a number of issues require additional research before oral pre-exposure prophylaxis (PrEP) can be implemented on a large scale, according to an article in *AIDS Patient Care and STDs*, a peer-reviewed journal published by Mary Ann Liebert, Inc. ([www.liebertpub.com](http://www.liebertpub.com)). The article is available free online at [www.liebertpub.com/apc](http://www.liebertpub.com/apc).

After the success of a trial of PrEP in a high risk population of men who have sex with men (MSM), expanded studies are set to begin that will enroll more than 20,000 men and women. Although PrEP comprised of a two-drug regimen (the oral antiretroviral agents tenofovir and emtricitabine) was shown to be safe and effective in early clinical testing, Gavin Myers, MA and Kenneth Mayer, MD, Alpert Medical School of Brown University (Providence, RI) emphasize the need for more research in several key areas: the need for ongoing PrEP clinical monitoring of side effects; the diminished preventive benefits seen in patients who do not adhere to the PrEP regimen and the need for counseling; the attitudes and awareness of physicians who would be prescribing PrEP; and the potential for intermittent PrEP to be as effective as once-daily dosing. They discuss these issues in the article, "Oral Preexposure Anti-HIV Prophylaxis for High-Risk U.S. Populations: Current Considerations in Light of New Findings."

"This is an extraordinary example of translational medicine in the service of HIV prevention. But implementation faces major social obstacles. Adherence to a PrEP regimen is key. And the cost of the drugs may make it impractical for all but the highest at-risk populations," says Jeffrey Laurence, MD, Editor-in-Chief of the Journal and Director of the Laboratory for AIDS Virus Research at Weill Medical College of Cornell University (New York, NY).

Pushing HIV out the Door: How Host Factors Aid in the Release of HIV Particles

ScienceDaily (Mar. 13, 2011) — Human Immunodeficiency Virus (HIV)—which causes AIDS—invas human immune cells and causes them to produce new copies of the virus, which can then infect new cells. A research team led by Professor Don C. Lamb (LMU Munich) and Priv.-Doz. Dr. Barbara Müller of Heidelberg University Hospital have now analyzed the involvement of particular components of the infected cell in virion release, and discovered that the enzyme VPS4A plays a more active role in the process than was previously thought.

VPS4A was already known to act after virus budding was complete. Using an advanced microscopy technique, the group was able to show that complexes containing about a dozen VPS4A molecules form at points in the membrane at which newly assembled virions later emerge.

According to Lamb, "We can now demonstrate in detail, for the first time, how host proteins interact with components of HIV, to enable them to bud from infected cells. Our ultimate goal is to elucidate the entire life cycle of the virus. " "With the methods we have at our disposal, we can also study the effects of drugs on infected cells, which may allow us to improve their efficacy or even lead to the development of new classes of active compounds."

The research is published in *Nature Cell Biology*.

Viruses are like pirates: they board a suitable cell and alter its course to suit their own purpose. More specifically, they smuggle their own genetic material into a host cell and reprogram the cell to produce new virus particles. For release of the newly synthesized viruses, HIV exploits cellular proteins involved in the loading, sorting and budding of cellular vesicles known as ESCRT proteins. During budding, HIV makes use of ESCRT to cut the last connection between the virion coat and the cell surface, allowing it to exit the cell. The enzyme VPS4A forms part of the ESCRT machinery and is known to be necessary for the disassembly of the complex after use, allowing its components to be recycled.

The results from ultrasensitive live-cell imaging experiments showed that VPS4A also acts at an earlier stage in the budding process. In the new work, the researchers labeled the enzyme by fusing it with the Green Fluorescent Protein (GFP). This allowed them to track the protein in living cells. By recording the fluorescent signals, they observed how several VPS4A molecules came together to form larger complexes. "In this case, we were able to count how many enzyme molecules assembled at the HIV budding site during its interaction with the nascent virion" says Müller.

Complexes made up of about three dodecamers of VPS4A were observed to undergo transient activation (for about a minute) at a budding site. Shortly thereafter, the virions were observed to emerge...
from the cell at these locations. Because virion release does not follow immediately upon activation of the enzyme, the investigators believe that at least one further intermediate step is required for budding.

Perhaps this postulated step can be pinned down in a later project. "Our current methodology allows us to monitor the assembly of individual virions, and we are working on further refinements that will allow us to follow the complete life cycle of HIV," says Lamb. "We can already visualize some steps of the life cycle at the level of a single virus, observe interactions and determine the kinetics of different processes. Of course, this means that we can also label therapeutic agents and observe what effects they have in infected cells. This can help us to optimize the currently available drugs and even allow us to develop new ones."

The study was carried out in the context of three Clusters of Excellence, the Center for Integrated Protein Science Munich (CIPSM), the Nanosystems Initiative Munich (NIM) and CellNetworks Heidelberg. The work was also supported by the German Research Foundation (DFG) as part of Priority Program 1175 Dynamics of Cellular Membranes and Their Exploitation by Viruses.

Journal Reference:

By Stefan Kubicek

Infographic: Epigenetics—A Primer
There are many ways that epigenetic effects regulate the activation or repression of genes. Here are a few molecular tricks cells use to read off the right genetic program.

What makes the ~200 cell types in our body remember their identity? What prevents them from becoming cancer cells? Why do we inherit some traits from our father, others from our mother? How do our experiences and environment influence our thinking? Why do plants bloom in spring but not in winter? These important and quite different questions are all addressed by the field of epigenetics, which studies heritable changes in a phenotype arising in the absence of alterations in the DNA sequence. The idea of transgenerational inheritance of acquired characteristics goes back to Lamarck in the early 19th century, but still only correlative evidence exists in humans. In contrast, many cellular epigenetic phenomena are now well understood on the molecular level. In humans, they include the parent-of-origin specific expression of genes (imprinting) and the shutting-down of almost all genes on one of the two X chromosomes in females (X-chromosome inactivation).

All these epigenetic phenomena are characterized by chemical modifications to DNA itself (DNA methylation) or to histones, the proteins around which DNA is wound. These modifications change during development as stem cells give rise to liver cells and neurons, but also in response to environmental signals—in plants, for example, during the cold of winter or in humans when immune cells are activated after an infection. One of the biggest controversies in the field is whether histone modifications are inherited through cell division (called the “histone code hypothesis”) or whether they only form transient indicators of transcriptional states (“signaling model”).

Comment
Epigenetics: A Long Overdue Pre-Primer
by Dov Henis, [Comment posted 2011-03-01 23:28:40]
Science Should Adjust Its Vision, Comprehension And Concepts From "Think Again: Education", comment "Science In A Technology-Tradeunion Culture?" LINK Genes And Genomes Are Both Organisms Genomes Are RNA-Evolved Template ORGANISMS EpiDNAtics Is Not Epigenetics
From "Dispel Some Figments Of 2010 Science Imagination" [LINK]

The "heritable or enduring changes" are epiDNAtics, not epigenetics. Alternative splicing is not epigenetics, even if/when not involving alteration of the DNA sequence. Earth life is an RNA world. It's the RNAs that evolve proteins. AND IT'S THE RNAs THAT HAVE EVOLVED AND PRODUCE AND EMPLOY THE RNA and (stabler) DNA template genome organisms for carrying out life processes, i.e. for enhancing Earth's biosphere by proliferating RNAs, for augmenting and constraining as long as possible some energy by augmenting its, RNA's, self-propagation, constraining temporarily some of the total energy of the universe, all of which is nevertheless destined to fuel the ongoing cosmic expansion.

IT HAS ALWAYS BEEN AND IT STILL IS AN RNA EARTH LIFE.

Science should adjust its vision, comprehension and concepts.

Dov Henis
(comments from 22nd century) Seed of Human-Chimp Genomes Diversity [LINK 03.2010 Updated Life Manifest [LINK]

By Manel Esteller

**Epigenetic Changes in Cancer**

The study of how covalent marks on DNA and histones are involved in the origin and spread of cancer cells is also leading to new therapeutic strategies.

Much of the current hype in epigenetics stems from the recognition of its role in human cancer. Yet, intriguingly, the first epigenetic change in human tumors—global genomic DNA hypomethylation—was reported way back in the early 1980s, at about the same time the first genetic mutation in an oncogene was discovered. So why the delay in recognizing the importance of epigenetics in cancer?

In the 1980s epigenetics was a fledgling discipline, hampered by methodological limitations, while genetic knowledge of cancer was expanding exponentially. By the mid-1990s however, classical tumor suppressor genes, such as \( p16^{INK4a} \), \( hMLH1 \), and \( VHL \), were shown to undergo a specific epigenetic hit (the inactivation of gene expression by CpG island hypermethylation), resulting in a major acceleration in the field. We now know that so-called “epigenetic changes” explain many hallmark features of malignant disease: these genes are deregulated not at the DNA level, but at the complexity packaged chromatin level, which ultimately results in cell dysfunction.

**EPIGENETICS:** "The inheritance of patterns of DNA and RNA activity that do not depend on the naked nucleotide sequence. By “inheritance,” we mean a memory of such activity transmitted from one cell generation to the next (through mitosis)."

Epigenetics may be important for the cancer field, but what does the term really mean? Truth be told, it has many definitions, which have changed over the years as our knowledge has changed. Researchers studying this discipline recognize how bewildering such a nebulous term can be to nonexperts, and they get together from time to time to put forward better explanations and nomenclatures, but they usually come up empty-handed, or with recommendations that people do not remember. Thus, we have to go back to the classics. Waddington defined epigenetics in 1939 as “the causal interactions between genes and their products, which bring the phenotype into being.” Adrian Bird redefined the term as “the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states.” I prefer a more concrete definition: the inheritance of patterns of DNA and RNA activity that do not depend on the naked nucleotide sequence. By “inheritance,” we mean a memory of such activity transmitted from one cell generation to the next (through mitosis), or from one organismal generation to the next during meiosis. Meiotic inheritance is perhaps more provocative, as there is still scant direct evidence of epigenetic inheritance from one generation to the next, but genomic imprinting is a good example: when it goes awry it can lead to diseases such as Prader-Willi syndrome.

Epigenetics today is not a purely speculative subject, as it was in Waddington’s time; it is based on a rapidly growing understanding of the chemical modifications that our genome and its regulatory proteins (the components of chromatin) undergo to control its functions. There are many modes of epigenetic control, including nucleosome positioning and noncoding-RNA-mediated regulation of gene expression (such as microRNAs). (See infographic: Epigenetics—A Primer) Nucleosome positioning refers to the...
constraints nucleosomes put on the DNA wrapped around their histone core, often affecting the accessibility of transcription factors and hence their ability to transcribe a gene. The best-studied epigenetic marks, however, are DNA methylation and histone modifications.

In humans, DNA methylation typically occurs at the cytosine base of DNA, within CpG dinucleotides. What is interesting is the existence of CpG-rich regions—"CpG islands"—that are associated with the 5'-end regulatory regions of almost all housekeeping genes as well as with half of tissue-specific genes. When these promoter CpG islands are methylated, the associated genes tend to be transcriptionally inactive. Indeed the correct expression of many tissue-specific, germline-specific, imprinted, and X-chromosome inactivated (in females) genes, as well as that of repetitive genomic sequences, relies largely on DNA methylation.

Distinctive cancer-associated patterns of CpG island hypermethylation are tumor type-specific and contribute decisively to the origin and development of human cancer.

The other critical epigenetic marks are chemical modifications of the N-terminal tails of histone proteins. Histones, once considered mere DNA-packaging proteins, regulate the underlying DNA sequences through complex posttranslational modifications such as lysine acetylation, arginine and lysine methylation, or serine phosphorylation. It has been proposed that distinct combinations of modifications presented on histone tails form a "histone code" that regulates gene activity. This has prompted vigorous debate, with dissenters arguing that patterns of histone modification cannot really constitute a "code" that adheres to hard and fast rules, as in the case of the triplet codon rule that translates transcribed DNA sequences into protein. Nonetheless, for many epigenetic researchers this is a helpful perspective in trying to make sense of the numerous combinations of histone tail modifications.

A central question in epigenetics is how one genotype can give rise to different phenotypes. In an individual, it is clear that all tissues have the same genome, yet activity varies vastly from cell to cell. We now know that this is largely because the right epigenetic marks instruct specialized programs that distinguish, for example, a retinal cell from a myocyte, a T lymphocyte, or a skin epithelial cell sharing the same DNA sequence. Thus, defects in cloned animals could be explained by our inability to replicate exactly the epigenetic program that steered the course of development in the donor individual. Similarly, defects in babies conceived by in vitro fertilization could be attributable to imprinting variations leading to imprinted disorders. DNA methylation and histone modifications even seem to explain the different penetrance of diseases displayed in monozygotic twins, as first reported in one of our papers. This work has occasionally prompted inquiries from police or lawyers, asking whether we can assist in differentiating one identical twin from his or her sibling in court cases.

An epigenetic mutant-mouse strain illustrates how even diet can alter phenotype via an epigenetic mechanism: a DNA methylation variant mouse (agouti strain) changes fur color depending on the levels of methyl donors obtained through its diet, and the trait is heritable to the next generation. These discoveries actually restore some credibility to Lamarck's discredited hypothesis of the inheritance of acquired traits, which has long been regarded as the antithesis of neo-Darwinian genetic theory.

Many cancer scientists have gotten aboard the epigenetic bandwagon since new, user-friendly PCR- and sequencing-based technologies have been developed. The list of tumor suppressor genes shown to undergo epigenetic inactivation has consequently grown long in the last few years. And in addition to the candidate-gene approach, array-based techniques have also detected on the order of 300 epigenetically modified genes in cancers, using expression arrays combined with DNA demethylating treatments or direct DNA methylation microarrays. (See graphic below.)

Epigenetic disruption of the "dark genome"—the 90% of our genome that does not code for messenger RNA and proteins—is a very exciting finding that looks to be extremely relevant in cancer etiology. MicroRNAs with growth-inhibitory functions, such as miR-124a and miR-34b/c, undergo epigenetic inactivation because the sequences surrounding their respective transcription start sites become hypermethylated. Overall, the emerging picture shows that distinctive cancer-associated patterns of CpG island hypermethylation are tumor type-specific and contribute decisively to the origin and development of human cancer.

Besides providing a better understanding of cancer at the molecular level, what hope does epigenetics bring to applied cancer research? Epigenetics has already revealed useful diagnostic (GSTP1 in prostate cancer) and prognostic biomarkers. This has been an eye-opener for oncolgists and hematologists, as transformed cells with specific hypermethylation patterns on certain genes have turned out to be reliable biomarkers for particular types and stages of cancer. The best example is the aberrant DNA methylation of the GSTP1 gene, almost exclusively observed in prostate cancer, which seems to be a valuable biomarker for indicating the disease and a malignant transformation prognosis in older males with high
levels of prostate-specific antigen. The fact that these epigenetic markers can be detected in all types of biological fluids and biopsies in a background of many normal cells makes them very promising tools for disease screening and monitoring. With the advent of genome-wide methodologies, researchers are currently working on typing whole aberrant DNA methylation fingerprints. Such expression microarray signatures could, in the future, serve as potential prognostic tools, which could indicate time to progression or overall survival. This research is being done in breast cancer; however, clinical application is still years away.

Another invaluable use of epigenetic markers is in the prediction of responses to particular chemotherapy agents. The proof of principle was provided by the DNA repair enzyme MGMT, which, when the gene’s promoter region was hypermethylated at its CpG island, predicted that treatment with alkylating agents such as carmustine or temozolomide in gliomas would generate a good therapeutic response. This is because MGMT repairs the lesions caused by these drugs, and if the enzyme is not there, as in cancer cells, the DNA damage is permanent and the cell dies.

**USING EPIGENETICS TO FIGHT CANCER**

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<thead>
<tr>
<th>Area</th>
<th>Examines</th>
<th>Information</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Epigenetic markers</td>
<td>• DNA methylation patterns</td>
<td>GSTP1 gene in prostate cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Histone marks</td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>Changes in epigenetic markers over time</td>
<td>• Comparative patterns</td>
<td>p16INK4a gene in colon cancer</td>
</tr>
<tr>
<td>Pharmacogenetics</td>
<td>Methylation and gene expression profiles</td>
<td>• Fuller picture to predict drug response</td>
<td>MGMT gene in glioma</td>
</tr>
<tr>
<td>Drug Targets</td>
<td>• Epigenetic marks (DNA/histones)</td>
<td>• Add/read/remove epigenetic marks</td>
<td>5-Azacytidine</td>
</tr>
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<td>• Epigenetic marks</td>
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Potential treatment strategies for breast cancer in carriers of mutated *BRCA1*, the classical tumor suppressor gene, have been boosted by pharmacoepigenetics—the study of epigenetic variants that affect the response to drug therapies. The population of mutated *BRCA1* carriers is low; thus, the discovery that *BRCA1* can exist as an epimutant when hypermethylated has increased the pool of individuals affected by this high-risk, cancer-causing aberration. This is accelerating the development of the use of PARP (poly [ADP-ribose] polymerase) inhibitors, known to have a good response in *BRCA1* tumors.

The widespread use of high-throughput technologies will produce comprehensive cancer epigenomes to study and employ in the better management of oncology.

Histone modification patterns are also altered in human tumors. In particular, levels of histone H4 lysine 20 trimethylation (H4K20me3) and histone H4 lysine 16 monoacetylation (H4K16ac) are severely disturbed in cancer cells both globally and at particular loci. Comparing absolute results between laboratories, however, is proving troublesome, since the central technique—chromatin immunoprecipitation—has more interindividual and interlaboratory variation than the usual DNA methylation assays, and depends largely on the quality of the antibodies used. Thus the community is not yet at a stage where it can use altered histone modification profiles found in cancer as biomarkers. Researchers are, however, finding an increasing number of histone modifier genes disrupted in many cancers, opening the door to small-molecule drug development targeted against aberrant histone modifiers. This is particularly applicable to hematological malignancies and sarcomas, in which translocations that generate fusion proteins involving histone methyltransferases and histone acetyltransferases are common. The approach is also relevant for the gene amplification of histone demethylases in solid tumors.

A strong selling point for epigenetic cancer research is the fact that epigenetically inactivated genes can conceivably be reactivated with the right drugs, while genetic changes are irreversible. To date, a few pharmacological compounds directed toward epigenetic enzymes have shown promise in treating leukemias and lymphoma. These include DNA demethylating agents (5-azacytidine and 5-aza-2’-deoxycytidine) and histone deacetylase inhibitors (i.e. suberoyl anilide bishydroxamide, SAHA). Although their exact antitumor mechanism has not been completely elucidated, most of them cause programmed cell death and, at current doses, show limited toxicity in patients. The translation of these advances in hematological malignancies to solid tumors is slow, and it will be critical for ongoing studies to identify markers of good response to epigenetic drugs. New compounds continue to be developed in
preclinical research, targeting other histone modifiers, such as the class of histone deacetylases called sirtuins. Researchers are on the lookout for more specific DNA demethylating agents that do not change normal DNA methylation.

Cancer epigenetics is an exciting field as we continue to discover new types of epigenetic marks and levels of epigenetic control. Recent examples include the newly discovered 5-hydroxymethylcytosine modification; the chemical modification of RNA; the existence of important regulatory regions outside the minimal promoter, such as CpG island shores and enhancers; the role of chromatin remodeling factors that move nucleosomes around using ATP; and, most importantly, the epigenetic layers present in the noncoding RNA genome. The widespread use of high-throughput technologies will in a short time, I am sure, produce comprehensive cancer epigenomes to study and employ in the better management of oncology patients. Glimpses can already be seen in the publication of, for example, small-epigenome characterization and whole-genome DNA methylation analyses.

**New Technologies For Studying Epigenetic Marks**

To date, techniques employed to study epigenetic marks have provided mostly snapshots of DNA methylation and histone modification patterns for selected genomic regions of interest in particular cell types. Deciphering the entire epigenome is a major task that will contribute to the understanding of fundamental biological processes such as development, differentiation and disease. Precise mapping of the entire epigenome is a feasible goal now that the speed of sequencing and the resolution of array-based technologies have dramatically increased (and become cheaper to perform). Next-generation high-throughput sequencing platforms typically being used include the Solexa (Illumina), 454 (Roche) or SOLiD (Applied Biosystems).

The generation of a cell’s genome-wide DNA methylation profile—its methylome—is leading the charge in epigenomics since only one type of epigenetic modification need be identified. Techniques largely use bisulfite pre-treatment to distinguish a methylated CpG from an unmethylated one, followed by DNA sequencing. Deep sequencing of bisulfite-treated DNA defines the gold standard of methylome analysis. Even bisulfite reactions, however, are benefiting from technological advances: Johns Hopkins researchers have developed a protocol they call “methylation on beads” (MOB) which is conducted in a single test tube and minimizes time and sample loss by tethering DNA to silica superparamagnetic beads.

To make budgets stretch further, technologies have been developed that do not necessarily require massive parallel sequencing of the entire genome for each experiment. An interesting method is reduced-representation bisulfite sequencing (RRBS). DNA is first digested with methylation-insensitive enzymes, followed by deep sequencing of bisulfite-treated DNA of a length calculated to contain at least one informative CpG in each read. Another genome-wide profiling method, which is array based, is the new HumanMethylation450 BeadChip array from Illumina. It covers 99% of Refseq genes and more than 450,000 CpGs, including shores and shelves.

An exciting development in the technology of methylome analysis is PacBio’s new SMRT (single-molecule, real-time) DNA methylation sequencing system which supposedly distinguishes cytosine from methylcytosine (mC) and the new player, hydroxymethylcytosine (hmC), without the need of a bisulfite reaction. Given that there are only approximately 12 platforms in operation, it is still too soon to ascertain the single-base-pair accuracy of mC and hmC detection.

Chromatin immunoprecipitation (ChIP) is a classic indirect method of determining histone modifications in addition to DNA methylation. A fundamental limitation of this basic technique is the quality and specificity of the antibodies used. Groups of researchers are working to better report and catalog good antibodies. Methods coupled to this core protocol include high-resolution arrays (ChIP-on-chip) or deep sequencing of isolated DNA (ChIP-seq). Methylated DNA immunoprecipitation (MeDIP) represents a special variant using an antibody that recognizes methylated cytosine, which can subsequently be analyzed by arrays or sequencing. This method has classically been used to identify differentially methylated regions (DMRs) between samples. Other technological frontiers being explored are the identification of multiple histone modifications in one reaction, and methods to catalog and display the increasing amount of data generated by epigenetic studies. Groups of researchers are working on the latter, including NCBI’s Epigenomics Sample Browser and the Structural Genomics Consortium Web server.

While these variations on a theme depend on whether you want genome-wide information or deep sequencing of regions of interest, new technologies are key to cracking open the secrets of the epigenome.

—Manel Esteller
References:

Missing reference on DNA methylation of tumors
by miguel gama, [Comment posted 2011-03-14 11:27:09]
In your article you missed our early reference also from 1983 describing the levels of DNA methylation on tumors. It was part of my PhD dissertation and I am very disappointed to have it not included in this article. For your reference the citation is:

Complicated
by anonymous poster, [Comment posted 2011-03-12 18:41:38]
Is every tumor cell the same or heterogeneous with regard to "epigenetics". If so it could get very complicated, perhaps so complicated that nothing makes sense.

definition
by Jerry Jones, [Comment posted 2011-03-01 13:21:18]
I'm not sure I'd agree with your definition since the patterns that is inherited may not matter as much as the probability of expressing that pattern.

I do think this article is a much better primer than the one to which it is referring but falls prey to the same problem as mentioned...that is, there is a particular concept of "epigenetics" discussed with the pitfalls of group-validated standards of explanation.

By Andrew D. Ellington

Epigenetics and Society

Did Erasmus Darwin foreshadow the tweaking of his grandson’s paradigm?

The potent wish in the productive hour
Calls to its aid Imagination’s power;
O’er embryon throongs with mystic charm presides,
And sex from sex the nascent world divides...
—Erasmus Darwin,
“The Temple of Nature,” Canto II

I was first introduced to Charles Darwin’s flamboyant grandfather when I was an undergraduate searching through Michigan State’s wonderful Special Collections. In between bothering the curators for archived copies of Howard the Duck, I read Erasmus’s prose and poetry, and was treated to a great mind grappling with ideas that presaged one of the truly great ideas of modern times, the theory of evolution. As the passage above hints, Erasmus believed that environmental influences, in particular the “Imagination” of the parents, greatly influenced the phenotype of the child.

How very pre-Victorian (and post-). Erasmus anticipated Charles in many ways, but surprising results in the field of epigenetics—heritable (and reversible) changes in gene expression—suggest that he may...
have been very far ahead of his time indeed. In the current issue, David Berreby cites the increasing body of work that correlates childhood trauma with DNA methylation with suicide. One’s personal epigenome is modified by environmental perturbations, and that influences behavior. Certainly the Victorians could have related to the notion of an Original Sin that made its heritable mark on the genomes of parents created innocent, passing the curse down to their descendants. That said, the Victorians did have their biases, and it was of course the father who had the predominant influence over the child. But recently published studies of genetic imprinting show that the two parents’ influence on their offspring is more akin to a tug of war.

The Lamarckian idea that giraffes’ reaching for leaves resulted in longer-necked progeny seems silly to us today, primarily because we know so very much about the underlying mechanisms of genetics. And yet Lamarck may have a last laugh—think inheritance patterns in ciliates, or the effect of diet on the coat color of agouti mouse offspring. We are in the midst of a paradigm shift in our understanding of how evolution can act…on evolution, yielding mechanisms that allow both adaptation and heritability within the course of a lifetime. And such paradigm shifts almost always have societal consequences. Manel Esteller shows that epigenetics also impacts the "dark genome" in a way that may improve cancer diagnostics. An even more far-reaching consequence is that it may prove possible to engineer epigenetics, as Bob Kingston’s Thought Experiment tacitly suggests. If so, will epigenetic engineering be subject to the same restrictions as genetic engineering? Or will this be a way that we can not merely treat disease, but possibly engineer human health into future generations?

Such possibilities will be the rational outcome of a great deal of research and debate that is yet to come. However, there are at least two outcomes of the revolution in progress that would seem to have more near-term consequences. First, the overturning of a purely Darwinian paradigm will undoubtedly be viewed as the overturning of Darwin and his Theory itself. It matters not a whit that science will have been shown, once again, to be self-correcting, and to provide a means of advancing knowledge through the application of the experimental method and mechanistic naturalism. We can expect that epigenetics will be held up as the forerunner of that bastard child of Creationism, Intelligent Design. Dribs and drabs of this are already appearing on the Interwebs, but it may soon come to a school board near you. Second, the notion that environmental tags are embedded in our genome within a human time frame has got to be one of the best things to happen to tort law in a long time. DNA typing has led to the conviction of the guilty and the freeing of the innocent. Epigenetic typing may now lead to expert testimony regarding the presymptomatic impact of environmental disasters on susceptible populations. This may seem fanciful, but where there are moneyed interests (on either side), the science will inevitably follow.

The Reality of an Organism
by Dr HP Pandey, [Comment posted 2011-03-01 23:26:48]
An organism is the expression of sum total of interactions between its genotype and environment. Truly speaking, genotype and environment are the deciding factor of phenotype of each and every living being. Fundamentally the there are two families of genes; 1. Constitutive or Housekeeping genes and 2. Luxury or Temporal genes in which the former is regulated by feedback mechanism and is least affected by environmental fluctuations, however, the latter is controlled by environmental complexes; may be internal or external. In my opinion the whole of the Epigenetic story is controlled by the luxury or temporal components of the genome which are Time & Space specific in deciding the phenotype of an organism.

As always, C. Darwin was right on
by Ernest DuBrul, [Comment posted 2011-03-01 11:51:50]
Time to go back to your copy of The Origin, preferably one of the later editions. Ol’ Charlie himself held on to acquired characteristics as a way to generate diversity, even going so far as to use giraffe necks as an example. He was especially convinced of the environmental effects in causing blindness in cave animals. So, let me make a prediction: Future epigenetic research will verify Darwin’s ideas and an epigenetic cause of the initial blindness in cave fish will be discovered.

By Robert E. Kingston

The Mark of Faith
Testing a central tenet of epigenetic regulation
A fundamental problem in biology concerns how the genomic information present in fertilized eggs can give rise to the full spectrum of stably differentiated cell types required to form vertebrates and invertebrates. In the 1930s, C.H. Waddington's largely observational mammalian embryology studies, which defined this problem, were central to establishing the field of epigenetics. It is now well known that there are master regulatory genes that must be kept on to specify a given cell lineage and off in the many other cell lineages that make up the body.

The problem of keeping these genes in the off state when required has received considerable attention, in large part due to the landmark genetic studies initiated by Pam and Ed Lewis in the 1940s that identified a set of genes required for this repression. This family of genes is called the Polycomb
Group (PcG) because the visual phenotype of a heterozygous null allele in these genes is duplication on the second and third legs of the sex combs that wild-type male Drosophila flies have on their front legs. It turns out that PcG proteins repress key developmental master regulatory genes in organisms from plants to humans. The PcG is responsible for a diversity of important biological events, from why plants flower only in the spring (and not in a December warm spell) to how mammals form the correct body tissues in the correct locations.

Based on C.H. Waddington, The strategy of the genes, 1957; Antagain / Istockimages.com (mouse); Lucy Reading-Ikkanda (landscapes)

**Polycomb and histone methylation**

Study of the PcG has converged with another active area related to epigenetics, the study of covalent modification of histones. The four core histones wrap DNA around them to form a nucleosome, and every gene is bound by nucleosomes, usually at one nucleosome for every ~147 base pairs of DNA. A physical mark on histones is one possibility for how regulatory information might be transmitted from an already differentiated cell to a daughter cell. For example, a covalent mark specifying repression might be found on the histones that coat a specific gene in a liver cell, and these histones might retain the repressive covalent mark when new nucleosomes are formed after DNA replication. One of the key protein complexes formed by the PcG gene products, Polycomb repressive complex 2 (PRC2), methylates lysine 27 of histone H3 (H3K27). This mark is widely believed to be an important component of epigenetic mechanisms and is believed to function by creating a binding pocket for another PcG complex (PRC1) that effects repression.

The fact that a hypothesis makes sense does not eliminate the need to test it as rigorously as possible. Yet many who work on gene regulation are skeptical that methylation of lysine 27 confers epigenetic information—in this instance meaning information that is heritable and transmitted from mother to daughter cell to specify that a master regulatory gene be kept off. Significant issues with the model include whether the marked histones are faithfully replaced on the gene following replication, whether the energy created by a binding pocket constituted by a methyl group is sufficient to do the repressive job, and whether placement of the methyl mark can be accomplished with sufficient accuracy to effect defined regulation.

In comparison, gene-specific DNA binding proteins, known to play a role in epigenetic regulation, bind to their sites with energies considerably more formidable than can be created by a methyl mark on a histone. These proteins recognize specific DNA sequences that are lengthy enough to be unique within the genome, and one can easily imagine that the proteins will rebind accurately to those sequences following replication and cell division.

**Mutating histones in large eukaryotes**

There is a simple experiment that would go a long way toward addressing the concerns about the role played by covalent histone modification in heritable repression: mutate lysine 27 of histone H3 to arginine or to alanine. These substitutions would each prevent methylation by PRC2 and would be strongly predicted to impair development of an organism as observed either by gross phenotype or by a molecular phenotype such as RNA expression pattern. Put differently, if methylation of lysine 27 is a central
mechanism for PcG-based epigenetic regulation, eliminating the ability of an organism to perform this function should derail the PcG and thereby derail appropriate epigenetic repression of master regulatory genes.

This experiment is somewhat complicated to design at the conceptual level. There are many mechanisms that can contribute to epigenetic regulation, including sequence-specific binding factors, DNA methylation, and noncoding RNAs, and it is anticipated that each different master regulatory gene will use a different combination of these mechanisms—and that many of these mechanisms will be redundant. Thus it is unclear how many genes, and which ones, might rely upon methylation of H3K27. It is even possible, though unlikely given the multitude of mechanisms involved in regulating development, that H3K27 mutation might be lethal at such an early stage that study is difficult. A further complicating issue is that this mark might be required in acute repressive settings in the developing organism (e.g., in the rapid response to a precise developmental cue), and thus there might be impacts on development that have to do with this type of acute response rather than with epigenetic memory of the repressed state. Thus, one would ideally like to follow any affected gene in time across cell divisions to determine to what extent there is a defect in memory of a repressed state.

These conceptual issues can be tackled, but there are two other major roadblocks to doing this experiment—one technical and one motivational. The technical issue is that the organisms that would be most suitable for doing this experiment—Drosophila and mice—have numerous genes for histone H3 (more than twenty in each organism). It is very hard, therefore, to mutate all the endogenous genes, and technologies with which one might eliminate the endogenous genes via large deletions or RNAi have the issue of expressing a mutated replacement gene at the correct level. Gene manipulation techniques are continually expanding, however, and recent advances make this experiment feasible in flies (EMBO Reports 11:772–76, 2010).

The motivational issue is worrisome—on two levels. Even in flies, where the experiment is feasible, it will take a lot of work. But more to the point is the experience of one investigator who recently recounted that he was asked repeatedly why he would waste time doing an experiment that is so hard when everyone already knows the answer. The received wisdom is that of course methylation of lysine 27 is critical for epigenetic regulation: Isn’t it usually called an epigenetic mark? This reliance upon what is essentially an act of faith—methylation of histones makes sense as a mark that might be epigenetic, therefore it must be—is dangerous to progress. The fact that a hypothesis makes sense does not eliminate the need to test it rigorously as possible. Hopefully, mammalian technologies will advance so that point mutation of residues perceived to be epigenetic can in fact be performed, because the spectrum of mechanisms that govern these issues is not the same in flies and mammals. Until such definitive experiments are performed, skeptics will have free run, and the field will continue to spin its wheels.

By Frederick Grinnell

The Evolution of Credibility

The winding path that an interesting result takes to become a bona fide discovery is just one of the topics covered in this new book on the practice of science.

When I was a graduate student in biochemistry at Tufts University School of Medicine, I read an abridged version of Montaigne’s Essays. My friend Margaret Rea (a.k.a. Marci Trindle) and I spent hours wandering around Boston discussing the meaning and implications of the essays. Michel de Montaigne lived in the 16th century near Bordeaux, France. He did his writing in the southwest tower of his chateau, where he surrounded himself with a library of more than 1,000 books, a remarkable collection for that time. Montaigne posed the question, “What do I know?” By extension, he asks us all: Why do you believe what you think you know? My latest attempt to answer Montaigne can be found in Everyday Practice of Science: Where Intuition and Passion Meet Objectivity and Logic, originally published in January 2009 and soon to be out in paperback from the Oxford University Press.

Scientists tend to be glib about answering Montaigne’s question. After all, the success of technology testifies to the truth of our work. But the situation is more complicated.

In the idealized version of how science is done, facts about the world are waiting to be observed and collected by objective researchers who use the scientific method to carry out their work. But in the everyday practice of science, discovery frequently follows an ambiguous and convoluted route. We aim to be objective, but we cannot escape the context of our unique life experiences. Prior knowledge and interests influence what we experience, what we think our experiences mean, and the subsequent actions we take. Opportunities for misinterpretation, error, and self-deception abound.
Consequently, discovery claims should be thought of as protoscience. Similar to newly staked mining claims, they are full of potential. But it takes communal scrutiny and acceptance to transform a discovery claim into a full-fledged discovery. This is the credibility process, through which the individual researcher’s me, here, now becomes the community’s anyone, anywhere, anytime. Objective knowledge is the goal, not the starting point.

Once a discovery claim becomes public, the discoverer receives intellectual credit. But, unlike with mining claims, the community takes control of what happens next. Within the complex social structure of the scientific community, researchers make discoveries; editors and reviewers act as gatekeepers by controlling the publication process; other scientists use the new finding to suit their own purposes; and finally, the public (including other scientists) receives the new discovery and possibly accompanying technology. As a discovery claim works its way through the community, a dialectic of interaction and confrontation between shared and competing beliefs about the science and the technology involved transforms an individual’s discovery claim into the community’s credible discovery.

Two paradoxes infuse this credibility process. First, scientific work tends to focus on some aspect of prevailing knowledge that is viewed as incomplete or incorrect. Little reward accompanies duplication and confirmation of what is already known and believed. The goal is new-search, not re-search. Not surprisingly, newly published discovery claims and credible discoveries that appear to be important and convincing will always be open to challenge and potential modification or refutation by future researchers. Second, novelty itself frequently provokes disbelief. Nobel Laureate and physiologist Albert Szent-Györgyi once described discovery as “seeing what everybody has seen and thinking what nobody has thought.” But thinking what nobody else has thought and telling others what they have missed may not change their views. Sometimes years are required for truly novel discovery claims to be accepted and appreciated.

In the end, credibility “happens” to a discovery claim—a process that corresponds to what philosopher Annette Baier has described as the commons of the mind. “We reason together, challenge, revise, and complete each other’s reasoning and each other’s conceptions of reason,” she wrote in a book with that title. In the case of science, it is the commons of the mind where we find the answer to Montaigne’s question: Why do you believe what you think you know?

**Didn’t Michael Polanyi cover most of this?**
by Gene Godbold, [Comment posted 2011-03-01 10:36:10]
Check out “Tacit knowing, truthful knowing” on Amazon.

**The best Evolution of Consciousness**
by Alex Fedotov, [Comment posted 2011-03-01 02:50:03]
Dear Professor, Frederick Grinnell
A clear and straightforward about this idea in the development of consciousness I wrote 15 years ago in his work samooblikovannoj in his avfedotov.narod.ru and unfortunately received only one review in English of the scientist from St. Petersburg to nanotechnology. The anglijism language to write such a work can’t be and nikčenu because of different traditions and understanding of reality. But the essence will always remain one experience and experience of everyday scientific hermit trud—gi in science are different levels of generality and biology as science only begins its path of development will be a lot of ?poľkrytij and speculation until it is changed and he’s already method ? at sunrise that lit the horizon is analysis and synthesis of information on experiences past experimental data and computer simulation-bioinformacionμ. There will be many new and interesting discoveries including the problem of cancer where I toil as hermit consciously around 1965. But I would not want to focus on evidence that everything they see. The opening is what no one else saw. But his confession has been delayed due to public opinion "scientific conservatism" as this rather unscientific. And I will gladly read your work ? especially since I know almost all your work in the field of biology.

Best regards Alex Fedotov , Ass.Prof.in Moscow State University of applied biotechnology.

1 Mart 2011
Moscow.

?...may not change their views? by Richard Gordon, [Comment posted 2011-02-08 10:13:06]
...nor their willingness to approve grant funds to test new ideas. The peer review system is so often used to suppress innovation, that the ?truly novel discovery? often never enters the ?commons of the mind?, or is delayed so whole generations of the public who pay for it miss the benefits of its fruits. The benign view of science discourse presented above hardly fits reality. A funding system that recognizes and bypasses the resistance of those with entrenched ideas to new ones is sorely needed. We need democratization of science, not gatekeepers. Fortunately the Internet is rapidly replacing this old model, at least for scientific publication, if not yet funding.

-Richard Gordon, gordonr@cc.umanitoba.ca

**Intelligible Design**
by Richard Brown, [Comment posted 2011-02-07 08:30:03]
I was recently privileged to hear Professor Grinnell speak. The deapth of his thought about why we believe what we believe, and the clarity with which he communicates that thought, is evident in his short article, "The Evolution of Credibility". He clearly describes the transition from "me, here, now" to "anyone, anywhere, anytime". In the presentation I attended he elaborated on the more fundamental questions about the roles of God and science, about intelligible rather than intelligent design, and about the pathways to understanding as presented by philosophers and scientists, including many quotations from Einstein used to flesh out those
fundamental issues. For anyone wanting to explore the deep questions of science, God and philosophy in a clear, well reasoned manner, Fred Grinnell is an author to consider.

By Richard P. Grant

**Come Inside**

**The paper**

**The finding**
Antibodies work by activating the complement cascade, preventing invading microorganisms from entering cells, or binding to a pathogen and marking it for destruction by immune cells. Now, Leo James and colleagues at the MRC-LMB in Cambridge have discovered a fourth method that works inside cells, providing a “last line of defense” against infection.

**The ambush**
James’ lab observed that antibodies can remain bound to adenovirus as it infects cells. The result sparked their curiosity, because they had previously shown that the intracellular protein TRIM21 binds to the Fc region of antibodies with higher affinity than any other antibody receptor in the body.

**Animated Immunity**

*Watch antibodies neutralize viral invaders in this animation from the lab of Leo James*

**Credit:** Lesley McKeane, MRC Visual Aids

**The neutralization**
They found that TRIM21 adds ubiquitin to the adenovirus-antibody complex, targeting it for destruction by the proteasome. The finding “adds conceptually to the immune response,” says F1000 Member David Alpers.

**The patents**
TRIM21 only works if the virus doesn't shed the antibody as it enters the cell. This means it should be effective against all nonenveloped viruses, such as rotaviruses and noroviruses, which cause diarrhea and gastroenteritis. James’ lab is in the process of cataloging which infections retain antibodies, and looking for other TRIM21-like proteins. They are also trying to develop novel antiviral therapies, having already applied for patents covering the use of synthetic TRIM21 to treat infections.
By David Berreby

**Environmental Impact**

Research in behavioral epigenetics is seeking evidence that links experience to biochemistry to gene expression and back out again.

In the late 1970s, when Hans Reul was a student running gels on the rich soup of proteins around DNA and RNA, he found himself wondering about the function of those nongenetic molecules in his samples. “I asked my supervisor, ‘What are those proteins down there?’ he recalls. “And he said, ‘Well, they’re histone molecules. We have no clue what they’re doing. They sit in the nucleus and do something with the DNA.’”

At the time, for researchers chasing links between genes and behavior, all the tools and all the promise seemed to focus on two molecules, DNA and RNA. So did depictions in the popular media of the links between genes and personality. It was the era when Nobelist Walter Gilbert, extolling the Human Genome Project, would hold up a compact disc of data and tell his audience, “This is you.”

Today, it’s known that the “something” that histones and other proteins do with DNA includes turning genes on and off, or (more commonly) turning their expression up or down. Because DNA is tightly wrapped around the histones, chemical modification of histone proteins (for example, the addition of methyl or acetyl groups) alters gene expression. Moreover, methyl groups also attach to and detach from DNA itself—at discrete cytosines in the genome—and that also affects expression. (See infographic: **Epigenetics: A Primer**.)

**EPIGENETICS:** “An essential mechanism for pruning down the wide range of possible behaviors permitted by genes, selecting those that fit an individual’s environment.”

Two decades ago, neuroscientists were taught that DNA methylation events were immutable in nondividing adult neurons. Instead, says J. David Sweatt of the University of Alabama at Birmingham, methylation and demethylation are constantly happening in adult brain cells, where they are crucial for forming and maintaining memories. So Reul, who studies the effects of stress hormones on the brain at the University of Bristol, and Sweatt, who works on memory, spend much of their time these days thinking about gene transcription in the nucleus of the neuron. As neuroscientists, they never set out to “do epigenetics,” but epigenetics nonetheless has come to the sciences of brain and behavior. For Reul, Sweatt, and other investigators creating this new field of behavioral epigenetics, that CD of your genome isn’t you—at least not without a lot of additional data on the ways your experiences have affected the expression of those genes in your brain.

Behavioral epigenetics seems to demand a different conceptual mindset in neuroscience—a focus on molecular modifications in the cell’s nucleus.

In addition to short- and long-term memory, behavioral epigeneticists study trauma, children’s aggression, drug addiction, depression, and suicide, among other psychological issues. In those areas, say adherents, the epigenetic approach brings new tools, new concepts, new funding sources—and, many researchers admit, new hype—to the quest for the biological basis of psychology.

Geneticists working on suicide, for instance, have looked for alleles of particular genes that might predispose a person to kill himself. Neuroscientists look for an association between a behavioral pattern or character trait and an anatomical characteristic: for example, people abused as children tend to have smaller hippocampi than people who weren’t.1

Epigeneticists, though, focus on the up-and-down regulation of a gene’s expression, not on its differences from other alleles. And they’re interested in molecular events in the neuron’s nucleus, rather than the connections at its synapses—or the characteristics of functional brain regions.

Several years ago, for example, Moshe Szyf, Michael Meaney, Patrick McGowan and their colleagues compared the brains of 18 men who had been abused as children and later killed themselves to brains from 12 control subjects who had died suddenly of other causes and had no record of childhood trauma. Compared to the controls, the researchers reported in 2008, the suicides’ hippocampal tissue showed...
much higher degrees of DNA methylation in genes that encode ribosomal RNA. In another study the following year, they found that the brains of suicides who had not been abused as children didn’t show the same methylation pattern as those of suicides who had been: “there was no difference between nonabused suicide victims and controls.”

So Szyf and his colleagues believe they may have a first sighting of the ultimate goal of behavioral epigenetics: a precisely documented chain of connection from experience (child abuse) to measurable changes in gene expression in the brain (methylation of rRNA genes) to a behavior (suicide). “Although our findings are largely based on correlational studies indicating an association between psychopathology and methylation,” they wrote in their 2008 paper, “these data are consistent with growing evidence suggesting that alterations in cytosine methylation mediate biological processes associated with psychopathology.”

This kind of work raises the prospect of new drugs to treat behavioral disorders and new diagnostic methods, Szyf says: if a particular methylation pattern is tightly associated with vulnerability to suicidal thoughts, it might be possible to detect people who are at risk and intervene to help them.

Of course, taking cells from a living person’s hippocampus isn’t possible, and would be subject to ethical challenge. So some behavioral epigenetics labs have turned to blood assays, on the hypothesis that immune-system cells can serve as proxies for neurons.

“The immune system is highly interactive with the brain,” Szyf says, and he asserts that a number of labs have already “associated T-cell methylation with behavior.” The next question, he says, is: “If you can change behavior, will you also change T-cell methylation?” Richard E. Tremblay, of University College Dublin and the University of Montreal, with whom Szyf has collaborated, has been working on that question.

Tremblay and his colleagues recently analyzed blood samples from a cohort of boys, age 6 to 12, whose behavior suggested they were likely to become chronically aggressive, and compared them to more typical boys. The researchers’ preliminary analysis, Tremblay says, indicates that the high-aggression group tends, when compared to the more typical children, to have lower cytokine levels, and the genes that code for those cytokines, examined in T cells, have more methylated alleles. “The developmental pattern of these immune-system differences will be important to study,” Tremblay writes in an e-mail. “Are the differences in gene methylation and expression at the origin of the behaviour differences or are they the product of the behaviour differences?”

This sort of work illustrates why behavioral epigenetics seems to demand a different conceptual mindset in neuroscience—a focus on molecular modifications in the cell’s nucleus, rather than on interneuronal circuitry or gross anatomy. A 2000 study found that London cab drivers, who have to memorize a detailed map of a giant city, have larger-than-usual hippocampi—a correlation between anatomy and behavior that is a familiar type of neuroscience result, Szyf notes. But to his mind, the question it raises is: “Why is the hippocampus big?” Where are the instructions to grow encoded, and how are they triggered, at the level of DNA?

Epigenetics and memory

Of course, it has long been obvious that some sequence of physiological events must link a human being’s experiences to one’s DNA: people get depressed or develop a habit of violence because of biochemical signals in the brain that trigger molecular activity in the nuclei of neurons, shutting down some genes and increasing the activity of others. If that weren’t the case, people’s experiences could not affect their behavior.

What’s new and exciting, say the field’s boosters, is their recent progress in replacing this very general outline with biochemical details. Their goal, not yet reached, is to lay out every link in the causal chain that leads from a person’s experience to a neurotransmitter, then to a particular gene, then to a specific molecular modification of protein or DNA that affects that gene, and then back out from gene products to neuronal signaling to a person’s thoughts, feelings and actions.

The time scale—whether, for example, methylation lasts for the few hours of a short-term memory, for years as a long-term memory, or across generations as a tendency to get diabetes—isn’t the researchers’ main concern. C.H. Waddington’s founding definition of epigenetics—transgenerational inheritance that isn’t dependent on DNA sequence—doesn’t fit what they do.

The processes that modify DNA and histones “were originally described genetically because what was initially studied was transgenerational inheritance and patterns of variegated gene expression,” says Ted Abel, a molecular biologist at the University of Pennsylvania who works on the relationship of epigenetic processes to mental illness and neurodegenerative diseases. “But we now know the details of the
underlying biochemistry to these processes. So in my mind, the definition of what is considered an epigenetic process has expanded to include these biochemical mechanisms.”

Szyf thinks questions of heritability narrowly spotlight a single epigenetic time scale (what happens between generations), while methylation and demethylation occur at time scales ranging from seconds to hours (supporting short-term memories) to decades (supporting long-term memories), as well as generations. The emphasis on heritability is a cumbersome holdover from genetics, he says, “because in genetics, of course, everything is heritable. Do we want epigenetics to look like genetics? Why should we?”

At a conference last fall on behavioral epigenetics that attracted psychiatrists, psychologists, geneticists, anthropologists, neuroscientists, and molecular biologists, one of the organizers, Eric Nestler, a psychiatrist at the Mount Sinai School of Medicine, explained that behavioral researchers “are moving to a far broader definition of epigenetics which simply refers to any lasting change in gene expression mediated by an alteration in chromosomal structure.”

“Alterations in cytosine methylation mediate biological processes associated with psychopathology.”

If behavioral work is encouraging some molecular biologists to think less like geneticists, it is also encouraging neuroscientists to think differently about what they do. Like Reul, Sweatt came to epigenetics from work on neural systems. “When I finished my postdoc and started my own independent lab, I worked on signal-transduction mechanisms that are involved in long-term synaptic plasticity in memory formation,” he recalls. He and his colleagues found that mitogen-activated protein (MAP) kinases—the prototype regulators of cell division—known for their role in mitosis, differentiation, apoptosis, and other developmental processes—were also active in the long-lasting molecular changes in neurons that are crucial to long-term memory.

Other researchers were finding a role for growth factors and brain-derived neurotrophic factor (BDNF), among other regulators of cell growth, in making memories. And, in fact, methylation, “the direct chemical modification of DNA itself,” is also involved in memory formation, Sweatt says. He was intrigued. Adult neurons, after all, aren’t in the habit of dividing. So why were these “developmental” molecules so important to brain function? It sounded, he says, “like science fiction. After all, your DNA is not something you want to chemically covalently modify.”

One possible explanation, Sweatt says, is that learning and development aren’t all that different at the molecular level. Maybe, he says, “evolution has been efficient in the sense of using those mechanisms as part of developmental programming and then co-opting some of those same molecular mechanisms to subserve experience-dependent acquired behavioral change” (such as learning, memory, and long-standing habits) in adults. Szyf, too, speculates that behavioral epigenetics might end up showing that adult learning is simply development, continued. Perhaps, he says, “it’s all development, starting from preconception to death.”

Work in behavioral epigenetics also demands new frameworks for looking at the links between mind and gene, say people in the field. “We try to use genetics methodologies and concepts to study DNA methylation, and they just don’t fit. Methylation is a completely different beast, even though it’s in the DNA itself,” Szyf says.

For example, evolutionary biologists often speak of adaptation as synonymous with natural selection of genes—the winnowing process by which “less fit” genes disappear from a species’ DNA. In epigenetics, this concept of adaptation is useless: by definition, natural selection has already taken place, all the genes under study are “winners,” and the researchers’ goal is to see how variations in the expression of those genes produce variations in behavior. So, claims Szyf, genetic models—in which chemical changes are accidents occurring randomly, and inheritance is all—can’t explain epigenetic processes.

“Adaptation is not when everybody else dies and one guy survives,” he says. “Adaptation is when everybody adapts.” So, he argues, models that come from Darwinian natural selection won’t make sense for answering an epigenetic question. “We’re too obsessed with the Darwinian model,” he says. “And it blinds us from seeing a lot of what’s happening in nature that is not fitting that Darwinian model.”

That’s just the sort of grand rhetoric about behavioral epigenetics that annoys its critics, who complain that the excited claims of breakthroughs (especially in the popular press) have run far ahead of what is actually established.

In a recent editorial in the Journal of Psychiatry and Neuroscience, Paul Albert of the University of Ottawa divided his discussion of behavioral epigenetics into “hope” and “hype.” Among the reasons for a “hype” section, he cited two examples of maddening complexity in trying to establish links between the behavior of human beings and the behavior of molecules in their brain cells. At the psychological level of analysis, standardized measures of behavior are scarce. Diagnoses vary from psychiatrist to psychiatrist, and the same term for a mental illness may cover different symptoms. In
any large sample collected to study a mental illness, Albert writes, there are problems of “appropriateness of the ‘hyper-normal’ control group (screened for lack of mental illness and/or addiction), diagnostic variability, heterogeneity of illness and variations owing to mixed race, all of which will detract from the reliability and power of association.” Then, too, there are other mechanisms for fixing and maintaining a behavior—religion, law, tradition—which can confound attempts to link a behavior to a biochemical mark.

Meanwhile, at the molecular level, an epigenetic approach adds layers of complexity, in part because epigenetic marks don’t come simply in “on” and “off.” “For example,” Albert wrote, “typically individual DNA methylation sites are partially methylated; hence, multiple sequences from the same cell type or tissue preparation must be run to estimate the percentage of methylated nucleotides.”

For the moment, even its biggest advocates concede that behavioral epigenetics has yet to connect all its levels of analysis. It needs, and doesn’t yet have, at least one slam-dunk demonstration of all the links in a chain from behavior to neural activity to gene expression and back out again. How, for example, do biochemical events at a neuron’s nucleus affect the synaptic signaling between neurons that is the basis for all behavior? That, Abel explains, is an open question with many interesting possible answers.

“A lot of the experiments that are carried out in this field are correlative,” Abel says. “It’s research that’s looking at marks and how those marks change after a behavior. We’re doing experiments about necessity. We haven’t really done sufficiency experiments.” But, he notes, the whole field is only a few years old. Those types of experiments are on the drawing board, and the fact that much remains to be done is actually one of the attractions of the field.

“There are a lot of big open questions now that I think I probably won’t be able to answer to my satisfaction for quite a while,” Sweatt says. “I think I’m probably going to work on that for the rest of my career.”


References:

An HIV Strategy Invites Addicts In

By engaging high-risk populations and using antiretroviral therapy to suppress viral loads, thus inhibiting onward transmissions, health officials in Vancouver and British Columbia have helped curb HIV infection rates.

Vancouver’s supervised injection facility, Insite, is one reason why the city has been able to lower its HIV infection rate, experts say. Staff nurses at Insite provide injection drug users with sterile needles, condoms, gynecological exams, HIV screening, STD testing and treatment, and drug treatment referrals.

“There are fewer overdose deaths, less open drug use on the street, and we know it’s brought more people into detox,” said Dr. Patricia Daly, chief public health officer for Vancouver Coastal Health.

The number of provincial residents receiving HIV treatment jumped more than six-fold between 1996 and 2009. Now an estimated 80 percent of those infected, or 5,413 patients, receive treatment. The province’s test-and-treat policy has helped drive annual new infections down by 52 percent, even as both HIV testing rates and annual syphilis cases increased.

Similar results have been seen in San Francisco and Taiwan. In the United States, a three-year federal study of the test-and-treat model is being conducted in several locations, including the Bronx and District of Columbia.

“I went to the ministries of finance and health and told them: The best-kept secret in this field is that treatment is prevention,” said Dr. Julio S.G. Montaner, director of the British Columbia Center for Excellence in HIV/AIDS. For $50 million (US $51 million) spent on providing antiretroviral treatment, 400 infections down the line are averted, saving $300 million (US $308 million), he said.
The 800 injections that take place at Insite each day represent about 5 percent of injections citywide, officials estimate. A lawsuit to determine whether Insite can continue operating goes to Canada’s Supreme Court in May.

**Increased Rates of Bone Fracture Among HIV-Infected Persons in the HIV Outpatient Study (HOPS) Compared with the US General Population, 2000-2006**

*Clinical Infectious Diseases doi: 10.1093/cid/ciq242, (03.10.2011)  Benjamin Young; Christine N. Dao; Kate Buchacz; Rose Baker; John T. Brooks; and the HIV Outpatient Study Investigators*

Low bone mineral density is common among HIV patients, but data on their risk of fractures are limited, the authors wrote. To assess the risk, they analyzed data from HOPS, an open prospective cohort study of HIV-positive adults at 10 US HIV clinics, during 2002-08. Rates of fracture at any site were indirectly standardized to the general population by age and sex using data from outpatients in the National Hospital Ambulatory Medical Care Survey (NHAMCS-OPD). Investigators examined fracture-associated factors using Cox proportional hazards modeling.

Of 5,826 HOPS patients included in the analysis (median baseline age, 40 years; male sex, 79 percent; white race, 52 percent; antiretroviral exposed, 73 percent), 233 patients had incident fractures (crude annual rates, 59.6-93.5 per 10,000 persons). Standardized by age, fracture rates increased between 2000 and 2002 (P=.01), but stabilized in subsequent years.

Fracture rates and relative proportion of fragility fractures were higher among HOPS patients ages 25-54 than NHAMCS-OPD patients in the same age group. Incident fractures were associated with older age, substance abuse, nadir CD4+ cell count below 200 cells/mm3 (adjusted hazard ratio [aHR], 1.60; 95 percent confidence interval [CI], 1.11-2.31), hepatitis C infection (aHR, 1.61; 95 percent CI, 1.13-2.29) and diabetes (aHR, 1.62; 95 percent CI, 1.06-2.64).

“Age-adjusted fracture rates among HOPS patients were higher than rates in the general population during the period 2000-2006,” concluded the study authors. “Clinicians should regularly assess HIV-infected persons for fracture risk, especially those with low nadir CD4+ cell counts or other established risk factors for fracture.”

**Study shows importance of resistance testing before start of HIV treatment**

Michael Carter
Published: 15 March 2011

**One in ten Europeans already infected with drug-resistant HIV before starting treatment**

European research published in the February 28th edition of *The Lancet* shows the importance of considering the results of tests for transmitted resistance when selecting a patient’s first combination of antiretroviral drugs.

Individuals treated with a regimen which was not completely active were three time more likely to experience virologic failure during the first year than individuals with no resistance or those who had resistance but were treated with therapies to which they were fully susceptible.

There was also some evidence that baseline resistance impaired immune recovery.

“Transmitted drug resistance was associated with virological failure in patients who received at least one drug to which the virus had lost susceptibility,” write the investigators, who say their findings underscore “the need for at least three fully-active antiretroviral drugs to optimise virological response to a first-line regimen.”

In Europe, use of antiretroviral therapy has dramatically improved the prognosis of many patients with HIV. However, expanded use of HIV treatment has been accompanied by an increase in the transmission of drug-resistant HIV. Approximately 10% of all new infections in Europe involve a strain of virus that is resistant to at least one antiretroviral drug.

Resistance is the major reason why anti-HIV drugs cannot control viral load. European and British guidelines recommend that all patients should be tested for resistance soon after their diagnosis with HIV and again before they start antiretroviral therapy. First-line HIV therapy should take into account the results of this surveillance.

However, there is uncertainty about the impact of transmitted resistance on responses to first-line HIV treatment. This is especially the case if a patient with resistance takes a fully-active combination of drugs.
To gain a better understanding of this issue, European investigators examined outcomes in 10,000 patients who started HIV therapy after 1998. The patients were enrolled in 25 different adult and paediatric cohorts.

All the patients had a resistance test before they started therapy. Changes in viral load and CD4 cell count in the first year of treatment were examined.

The risk of virologic failure (two consecutive viral loads above 500 copies/ml after six months of treatment) was compared between patients according to whether they had no transmitted resistance; resistance, but treated with a combination of drugs that were fully active; transmitted resistance who therapy with a sub-optimal combination.

Approximately 10% of patients had transmitted resistance. Half were treated with antiretrovirals to which they were fully susceptible. The others received therapy to which they were at least partially resistant.

After a year of treatment, 4.2% of patients without transmitted resistance had experienced virologic failure. The rate was marginally higher (4.7%) for individuals with transmitted resistance who received therapy with three fully active drugs. However, a far greater proportion (15%) of patients with resistance and reduced susceptibility to a drug they received experienced virologic failure.

The investigators calculated these patients had a three-fold increase in their risk of virologic failure (p < 0.001).

Furthermore, patients with high-level resistance to the drug(s) they were taking had a six-fold increase in their risk of viral load remaining detectable or rebounding after six months of treatment (p < 0.001).

There was some evidence that therapy that included a ritonavir-boosted protease inhibitor was a good option for individuals with resistance who received fully active treatment. They were no more likely to experience virologic failure than individuals with no resistance who received this class of drug.

However, there was weak evidence of a higher risk of treatment failure for patients with transmitted resistance who received fully active treatment based on an NNRTI, compared to individuals with no resistance who were also treated with this class of drug (hazard ratio, = 2.0; 95% CI, 0.9-4.7, p = 0.093).

After one year of therapy, the median increase in CD4 cell count was 183 cells/mm³. There was modest evidence that patients with resistance who took therapy which was not fully active had smaller increases in their CD4 cell count during the first month of therapy. This was most apparent among patients who received an NNRTI (p = 0.0514).

"This finding is important because it suggests a poor immunological response in patients with transmitted drug resistance who are started on a suboptimum regimen will result in poorer CD4 response and ultimately risk of disease progression," write the authors.

They conclude, "this European observational multicohort study confirms present treatment guidelines that state that the initial treatment choice should be based on resistance testing in treatment-naive patients." In settings where resistance testing is not available, they suggest that a treatment based on a ritonavir-boosted protease inhibitor "should probably be considered."

**iTherX Initiates Phase 1b Study of First-in-Class Hepatitis C Virus Entry Inhibitor ITX-5061—Preclinical Studies Show that ITX-5061 Prevents Hepatitis C from Invading Liver Cells**

SAN DIEGO, March 15, 2011 /PRNewswire/ -- iTherX, a pharmaceutical company dedicated to discovering and developing a new class of therapies for hepatitis C, today announced that it has commenced patient recruitment in an open-label, proof-of-concept Phase 1b study of its lead compound ITX-5061 in liver transplant patients with hepatitis C virus infection (HCV). ITX-5061 represents a first-in-class compound that inhibits entry of the hepatitis C virus into liver cells.

"ITX-5061 possesses a unique mechanism of action that prevents the hepatitis C virus from entering liver cells and has demonstrated potent preclinical antiviral activity against all HCV genotypes. In addition, it has already demonstrated safety in more than 280 subjects," said Jeffrey McKelvy, PhD, MD, President and Chief Executive Officer of iTherX. "We hope ITX-5061 will significantly improve long-term transplant outcomes."

The primary objective of the Phase 1b clinical trial will be to assess the safety and tolerability of ITX-5061 in liver transplant patients. The study will also assess HCV viral load for three months after liver transplantation to determine if ITX-5061 has any immediate and/or sustained impact on viral kinetics in treated patients. Approximately 20 patients will be enrolled into one of two cohorts: one group will
receive supportive care only, while the second cohort will also receive ITX-5061 at a 150 mg daily dose for seven days. The trial is being conducted at the University of Birmingham, UK under the direction of David Mutimer, MBBS, MD, FRACP, FRCP, Reader in Hepatology at Birmingham University and Consultant Hepatologist to the Birmingham QE Hospital Liver and Hepatobiliary Unit.

Preclinical studies have shown ITX-5061 to be a potent and selective inhibitor of HCV entry into hepatocytes, capable of preventing virus binding/fusion and cell to cell spread, suggesting ITX-5061 may reduce re-infection rates following liver transplant.

"Recurrence of HCV infection among liver transplant patients is universal and immediate. Clinicians have long sought ways to prevent re-infection by HCV, improve transplant patient outcomes and extend survival," said Dr. Mutimer. "The potential of ITX-5061 to prevent or reduce viral infection of the new liver by halting viral-entry into healthy cells represents an extraordinarily novel approach, and we are excited to advance the clinical development of this promising antiviral compound."

The Phase 1b trial of ITX-5061 in liver transplant recipients is funded through an educational grant from iTherX with the National Institute of Health Research Biomedical Research Unit (NIH-BRU Birmingham).

This is a second clinical study for ITX-5061 in hepatitis C. The first study, a single agent placebo-controlled dose response study commenced in August 2010, is being conducted in treatment naive chronic HCV patients by the AIDS Clinical Trial Group of the National Institute of Allergy and Infectious Diseases.

About Hepatitis C

Hepatitis C virus (HCV) infection, a disease that attacks the liver, affects 170 million people worldwide. The majority of individuals develop chronic infection and up to 20 percent of infected individuals will develop cirrhosis with the attendant risks of liver failure and liver cell cancer. The current standard of care is combination antiviral treatment with pegylated interferon-alpha and ribavirin, which results in a cure for approximately half of all patients. Unfortunately, many patients present with clinically silent infection or advanced disease, at which time antiviral treatment is generally ineffective. For these patients, liver transplantation may be the only option. End-stage liver disease due to chronic HCV infection has become the leading indication for liver transplantation in the United States. Recurrence of hepatitis C virus after liver transplantation is inevitable and disease progression is rapid when compared with disease in the non-transplanted liver.

New Vaccine Candidate Shows Strong Potential To Prevent Highly Contagious Norovirus

COLUMBUS, Ohio – Scientists have shown that an experimental vaccine against the human norovirus – the bug behind about 90 percent of highly contagious nonbacterial illnesses that cause diarrhea and vomiting – can generate a strong immune response in mice without appearing to cause the animals any harm.

Using a novel viral vector-based method to grow and deliver the vaccine that has shown promise in other agents designed to fight such infections as HIV and hepatitis C, the researchers are the first to test this vaccine design method’s effectiveness against the human norovirus.

Animals receiving the vaccine developed high levels of antibodies, a robust white blood cell response and an additional immune response in the area of the body most affected by this particular infection – the gastrointestinal system.

The researchers say this study supports the use of viral vector-based techniques as a new way to develop vaccines for human norovirus and other viruses that cannot grow in cell cultures. It also suggests that these Ohio State University scientists could be well on their way to developing a safe vaccine against a highly problematic pathogen that causes millions of gastrointestinal illnesses every year in the United States.

“The mice in our study developed a much higher antibody response to our vaccine candidate than they did to a more traditional vaccine. That’s one of the keys, to have a sustained antibody response, so that when the disease comes along, you can neutralize the virus and protect yourself,” said Jianrong Li, assistant professor of food science and technology at Ohio State and senior author of the study.

Li co-authored the study with Yuanmei Ma, a graduate student in food science and technology. The research appears in the current issue of the Journal of Virology.

The Centers for Disease Control and Prevention estimates that more than 21 million cases of acute gastroenteritis – characterized by diarrhea, vomiting and stomach pain – each year are caused by
norovirus infection. Human norovirus is transmitted primarily through fecal-oral contact, either through contaminated food or water or direct person-to-person spread. This virus is famous for being so contagious that as few as 10 viral particles may be enough to cause symptoms. No vaccine or anti-viral drug is currently available for human norovirus.

That kind of pathogenic power makes the virus a high priority for vaccine developers, said Li, who also serves on Ohio State’s environmental health sciences faculty. But the process is complicated by two primary problems: The virus cannot grow in cell cultures, and no small animal models exist to mimic the infection.

Without the ability to grow the norovirus in cell cultures, the researchers instead inserted a human norovirus capsid gene – capsid refers to the virus’s outer shell – into a specific location on the genome of a different virus. This process creates what is known as a recombinant virus – a new viral strain formed by recombining genetic material from other viruses.

The viral host for this vaccine candidate is called vesicular stomatitis virus, or VSV, a bullet-shaped virus that has been an attractive vector for vaccine designers, Li said. The resulting recombinant viral vector functions as both the vehicle to deliver the vaccine as well as the agent that produces virus-like particles that mimic the human norovirus itself.

In this work, vaccination with the recombinant virus caused the norovirus capsid particles to grow continuously in animals, triggering a specific immune response. When the scientists tested these particles for their antigenic potential to look like foreign intruders in the body, the particles were neutralized by antibodies specifically designed to fight the human norovirus.

“So it looks like the virus and acts like the virus, but it’s not, and that is how a vaccine designed with virus-like particles should function,” Li said. “The virus-like particles can be continually produced in animals or humans for several weeks and stimulate strong immune responses. That’s the advantage of using VSV.”

Li said the VSV-based recombinant is also considered a powerful application because it can essentially be used as a bioreactor to facilitate large-scale production of these specific virus-like particles. In addition, it saves time: The viral vector developed virus-like particles within two days.

For comparison purposes in this study, Li and Ma also created a more traditional vaccine candidate by inserting a human norovirus gene into a different type of virus: a baculovirus, which is rod-shaped. It took six days for these viruses to grow enough to be used as a vaccine candidate, and the production level was comparatively low.

The scientists then conducted an animal study to observe what kind of immune response the VSV-based norovirus vaccine candidate could generate. Mice received either the VSV-based vaccine or various types of control substances for comparison, including one group that received the vaccine created with the more traditional technique. The substances were given orally or through the nose.

Weekly blood samples showed that two weeks after receiving the vaccines, the mice given the VSV-based norovirus vaccine had developed and sustained a high level of antibodies against the human norovirus – about 25 times higher levels of antibodies than those induced by the traditionally prepared vaccine candidate.

“This might be the most important advantage of the VSV-based norovirus vaccine candidate: It prepares a high concentration of norovirus-specific antibodies that can assist with virus detection, disease diagnosis and therapy,” Li said.

In addition, the mice vaccinated with VSV-based vaccine generated a T cell immune response that was two times higher than the T cell response produced in mice receiving the traditional vaccine candidate. The immune response involving T cells, a type of white blood cell, plays an important role in efficient clearance of norovirus infection.

Li said the mucosal immune response – that involving areas covered by mucous membranes – was similar in the two vaccine types the mice received. The scientists tested fecal samples and vaginal antibody levels in the mice, and found the levels comparable between the groups of mice receiving the two different types of vaccine.

VSV is known to infect animals, especially cattle and pigs. Human infection with VSV is very rare. The VSV-based norovirus vaccine led to minimal weight loss but caused no symptoms of illness in mice. This showed that the virus strain was attenuated, or had lost its ability to spread, because of the additional gene inserted into its genome, Li explained.

Because mice will not develop traditional norovirus symptoms, this study did not involve a test of the vaccine against the pathogen itself. Li said his further research plans include enhancing the vaccine candidate by inserting additional genes into VSV along with the human norovirus gene, which is expected
to make the vaccine more potent but still safe. And he then hopes to test the vaccine candidate in a larger animal model, such as so-called germ-free pigs, animals that have never been exposed to any pathogens. These animals develop diarrhea in response to norovirus infection, as do humans.

**HPV Linked to More Cancers; Prevention Strategy Could Include Male Vaccine, Says Oncologist**

*Toronto Star*, (03.07.2011)

Additional evidence tying human papillomavirus to anal, head, and neck cancers in both sexes, and to penile cancer in men, necessitates heightened preventive measures, according to Dr. Joan Murphy, a gynecological oncologist at Toronto’s Princess Margaret Hospital. “We need to look again at our publicly funded public health strategy and also our advice to individuals,” said Murphy.

A report in the Lancet, “Incidence and Clearance of Genital Human Papillomavirus Infection in Men (HIM): A Cohort Study,” indicated the virus, certain strains of which cause most cervical cancer cases, can be found in approximately 50 percent of all sexually active men.

Health Canada, which in 2006 approved an HPV vaccine for girls ages nine to 26 to stave off cervical cancer and genital warts, approved it in 2010 to prevent genital warts in young males. The United States also has approved vaccination of males ages nine to 26.

Murphy urges patients to speak with their care providers about the vaccine. “A proportion of men will benefit from the vaccine, not only from a genital warts point of view, but a cancer point of view as well. The science is not robust enough [in Canada] for approval to be given for use as a cancer indication, but it’s only a matter of time,” Murphy continued.

Although Ontario funds giving eighth-grade girls the three-shot vaccine, only 65 percent of them receive it. Other patients must pay $120 to $150 (US $122-$152) per shot.

Toronto Associate Medical Officer of Health Dr. Vinita Dubey believes including boys in a comprehensive vaccine push may be possible if the price comes down.

**Spatial Clustering of HIV Prevalence in Atlanta, Georgia, and Population Characteristics Associated with Case Concentrations**

*Journal of Urban Health Vol. 88; No. 1: P. 129-141*, (02..2011) Brooke A. Hixson; Saad B. Omer; Carlos del Rio; Paula M. Frew

In the current report, researchers studied prevalent HIV cases in Atlanta, examining distribution trends and population characteristics at the census tract level that may be associated with clustering effects.

Cluster characteristics (area and internal prevalence) were calculated using Kulldorff’s spatial scan method. Logistic regression analyses were performed to analyze sociodemographic variables associated with inclusion in a cluster. Researchers also identified locations of organizations offering voluntary HIV testing and counseling and assessed the average travel time to access the services.

The authors identified one large centralized cluster in downtown Atlanta that contained 60 percent of prevalent HIV cases. HIV prevalence inside the cluster was 1.34 percent, compared with 0.32 percent outside the cluster.

Clustered tracts were associated with higher levels of poverty (OR=1.19), lower density of multi-racial residents (OR=1.85), injection drug use (OR=1.99), men having sex with men (OR=3.01), and MSM and IDU (OR=1.6). Of Atlanta HIV service organizations identified, 42 percent were located in the cluster, and average travel time was 13 minutes by car (SD=9.24).

“The HIV epidemic in Atlanta is concentrated in one large cluster characterized by poverty, [MSM], and IV drug usage,” the authors concluded. “Prevention efforts targeted to the population living in this area as well as efforts to address the specific needs of these populations may be most beneficial in curtailing the epidemic within the identified cluster.”

**Hampton Roads Has Some of the Highest STD Rates in the Nation**

*Daily Press (Newport News)*, (03.09.2011) Veronica Chufo

Hampton Roads ranks near the top for certain STDs among US metropolitan areas, according to a 2010 CDC report. It ranked second-highest for chlamydia reports and third for gonorrhea, while Eastern Virginia has the state’s highest proportion of residents with HIV/AIDS.

“We have a significant local epidemic,” said Dr. Edward Oldfield, director of Eastern Virginia Medical School’s infectious-disease division. Engaging in unprotected sex therefore is riskier in Hampton Roads than in many other parts of the nation, said Oldfield, director of nine area HIV clinics.
Oldfield said these clinics see about one new HIV diagnosis per day. With sites in Williamsburg, Gloucester County, Norfolk, Virginia Beach, Portsmouth, and Chesapeake, the clinics treat about 2,000 patients total.

Of state HIV diagnoses in 2009, black residents comprised about 62 percent. Between 2005 and 2009, black residents made up 76 percent of gonorrhea reports, 63 percent of syphilis diagnoses, and 55 percent of chlamydia cases, according to the state health department.

Norfolk accounted for 9 percent of state chlamydia diagnoses between 2005 and 2009, while Newport News and Virginia Beach each accounted for 7 percent. In 2009, Norfolk had 11 percent of state gonorrhea diagnoses, while Newport News had 8 percent. Between 2005 and 2009, Norfolk and Richmond had 12 percent each of state syphilis diagnoses, while 5 percent were in Newport News.

Young black men who have sex with men are the most common demographic for HIV diagnoses, Oldfield said. Between 2001 and 2006, HIV diagnoses in black men ages 13-24 rose 93 percent, he said.

Unprotected receptive anal sex is “a very, very risky behavior, and I don’t think people know that,” he said. “It’s much higher risk than vaginal sex.”

As of March 10, 521 HIV-positive Virginians were on the waiting list of the state AIDS Drug Assistance Program.

Guatemalans Sue over 1940s US Syphilis Experiments
Associated Press, (03.14.2011)

Attorneys representing some Guatemalan victims of a 1940s syphilis experiment filed suit Monday to force US officials to compensate those affected. In the Guatemalan experiments—kept secret for decades, then discovered by a medical historian in 2009—some 700 prisoners, soldiers, mental patients, and orphans were deliberately infected with the STD by US scientists, who were studying the effects of penicillin. None were informed of the experiment or gave their consent to participate. The attorneys had given the Obama administration until last Friday to set up an out-of-court claims process under which the victims could seek reparations; the suit was filed when that deadline passed.

AIDS Drugs Slow Deaths in South Africa: Study
Agence France Presse, (03.11.2011)

South Africa’s rapid rollout of antiretrovirals has cut its AIDS death rate by almost 25 percent in recent years, according to a new model from the Actuarial Society of South Africa. In 2003, before ARVs were widely available, ASSA projected that AIDS would kill 388,000 South Africans in 2010. The new data, however, show the estimated number of AIDS deaths falling from 257,000 six years ago to 194,000 last year. Between 2005 and 2010, HIV infections dropped 1.5 percent among those ages 15 to 24. A 0.6 percent increase in HIV among those ages 15 to 49 during the same time period is believed due, in part, to patients on treatment living longer. The model does not take into account newer prevention initiatives such as the effort to expand male circumcision, which has been shown to reduce the risk of female-to-male HIV transmission by 60 percent, and last year’s efforts broadening treatment access. South Africa’s government, which for years had publicly denied the efficacy of AIDS medications, announced in December that 1 million patients were receiving treatment.

Normally tranquil Botswana has plunged into a fierce public debate about whether homosexuality is "un-African", sparked by a new lawsuit against the country's sodomy law.

Wedged between liberal South Africa, which allows gay marriage, and conservative Zimbabwe, where President Robert Mugabe regularly lambasts gays, Botswana has emerged as a testing ground for competing visions of African social values.

The court case was filed on March 4 by Caine Youngman, founder of a group called Lesbians, Gays and Bisexuals of Botswana (Legabibo), which the government refused to register in 2009.

He argues that the sodomy law violates his constitutionally protected freedom of expression, and he has won support from the Botswana Network on Ethics, Law and HIV (BONELA) and other civil forums.

"I never freely express my sexuality because of the law that criminalises sex between people of the same sex," Youngman said in an affidavit.

He originally announced the lawsuit two years ago, but delays in gathering paperwork for the court meant it was only filed early this month.
During that time, Botswana's gays received an unexpected—if cautious—voice of support from no less than former president Festus Mogae.

As head of the National AIDS Council, Mogae last year began speaking out against sexual discrimination, saying prejudice was hindering efforts to fight HIV in a country where one in four adults had the disease.

"We do not want to discriminate. Our HIV message applies to everybody," he said last year in his first remarks on the issue.

"If we are fighting stigma associated with sex, let's apply it to sexual discrimination in general."

He has continued speaking out, telling the BBC last weekend that during his 10 years in office he had instructed police not to arrest or harass gays.

"I could not change the law because that would be unnecessarily stirring up a hornet's nest. I was not willing to lose an election on behalf of the gays," he explained.

"The majority of our people are still opposed (to homosexuality) so I must convince them first before changing the law unilaterally," he said.

But the backlash has been vocal.

Parliament's deputy speaker Pono Moatlhodi told local media that gays were "demonic and evil" and had no place in African society.

"On this point I would agree with Zimbabwean President Robert Mugabe who once described that behaviour as that of Western dogs," he said.

"I don't like those gay people and will never tolerate them. They are demonic and evil."

Conservative religious leaders have also claimed that homosexuality runs against Botswana's culture.

"Our nation has done well to keep these legally and customarily unacceptable, and we must resist any suggestions that would lead to homosexual marriages in our nation," said Biggie Butale, head of the Evangelical Fellowship of Botswana.

Such intense debate is rare in Botswana, which prides itself on its stable democracy, but has few public disagreements with a largely homogenous population. The nation's diamond wealth is generally seen as well-managed.

Current President Ian Khama has straddled a middle line, saying he had no problem with homosexuals as long as they "do their things" behind closed doors.

Derision of gays as "un-African" infuriates Youngman, a 27-year-old inspired by the freedoms he sees across the border in South Africa.

"Enough is enough. Gays are Batswana, and were not made in a cocoon somewhere and put in this country to corrupt the Batswanas," he said.

"I need to be free in what I do. Gay people are no different from the rest of the nation and they deserve that freedom."

Rubaramira wants HIV/AIDS Bill shelved Tuesday, 15th March, 2011

By Josephine Maseruka and Henry Ssekanjako

RETIRED Major Rubaramira Ruranga who has lived with HIV/AIDS for the last 27 years has cautioned Parliament against making a punitive law on the epidemic.

"What Ugandans want is a law that will help in the epidemic, not a punitive one which will destroy all the gains the country has made," he said.

He made the remarks at a regional stakeholders' consultative meeting at Protea Hotel, Kampala last Friday.

The meeting, organised by the Uganda Human Rights Commission (UHRC), was aimed at reviewing the draft Prevention and Control of HIV/AIDS Bill 2010, which may be passed within the next 40 days.

It was attended by human rights activists, representatives of civil society organisations, people living with HIV/AIDS, UNAIDS and officials from the justice and health ministries.

Rubaramira wants the criminalising clauses in the Bill removed.

"There can never be a normal person who would try to kill or poison any other. Such suspected persons should be examined for psychotic disorders.

This Bill could cause these disorders if passed in its form," Rubaramira said.

There are adequate provisions in the Penal Code on transmitting infections.

Gonorrhea has existed for generations. How many people have been charged or imprisoned for infecting others?" he asked.
Rubaramira, who said he would never die of HIV/AIDS because of his sufficient knowledge on the disease, called for more sensitisation of the public on the epidemic.

The Bill aims at providing for a legal framework to prevent and control HIV and to reduce its transmission by creating offences for willful and intentional transmission.

Participants said if it was proved that someone willfully spread the disease, they must be charged under the Penal Code.

People living with HIV/AIDS said the law did not represent the people and should be shelved.

Civil society organisations want the name of the Bill to be changed to HIV management Bill with more emphasis on prevention and support programmes.

**US: State public health officials condemn 'stigmatising, harmful' HIV-specific laws**

This weekend, the National Alliance of State and Territorial AIDS Directors (NASTAD) released a statement that signifies an extremely important development in the Positive Justice Project’s campaign to repeal HIV-specific criminal laws in the United States.

NASTAD is a highly-respected organisation of public health officials that administer state and territorial HIV prevention and care programmes throughout the US.

Its motto is: 'Bridging Science, Policy, and Public Health'.

The message of their statement is simple: repeal these laws because HIV criminalization undercuts our most basic HIV prevention and sexual health messages, and breeds ignorance, fear and discrimination against people living with HIV.

In order to work towards the goal of repealing laws that create HIV-specific crimes or increased penalties for persons who are HIV-positive and convicted of criminal offences, NASTAD will advocate at the national level to raise awareness of this urgent issue. Realizing the vision of the NHAS is predicated on a strong foundation of public health science and practice void of stigma and discrimination. Instead of applying criminal law to HIV transmission, state and local governments should expand programs to reduce HIV transmission while protecting the human rights of people living with HIV.

Further, NASTAD encourages its members to:
- Support the maintenance of confidentiality of HIV test and medical records in order to encourage and support individuals to be tested, learn their status and enter services if positive;
- Identify and share best practices related to successes in repeal of policies and/or laws and statutes in jurisdictions that are not grounded in public health science; Promote public education and understanding of the stigmatizing impact and negative public health consequences of criminalization statutes and prosecutions;
- Provide unequivocal public health leadership on the relative risks of transmission and the dangers of a punitive response to HIV exposure on the epidemic.

Todd Heywood of the Michigan Messenger reports that US HIV advocates—including the National Association of People with AIDS (NAPWA) and the Positive Justice Project’s Senior Advisor, Sean Strub—have warmly welcomed NASTAD’s statement. Read his report at the Michigan Messenger here.

The full text of the statement, below, can also be downloaded as a pdf.

**National Hiv/AIDS Strategy Imperative: Fighting Stigma And Discrimination By Repealing HIV-Specific Criminal Statutes**

The National Alliance of State and Territorial AIDS Directors (NASTAD), the organization which represents the public health officials that administer state and territorial HIV/AIDS and adult viral hepatitis prevention and care programs nationwide is greatly concerned about the corrosive impact of sustained stigma and discrimination on state, federal and local efforts to combat HIV/AIDS in the United States. The National HIV/AIDS Strategy (NHAS) provides an unprecedented strategic blueprint for reducing HIV/AIDS incidence through the scale-up of interdisciplinary, impactful prevention approaches. NASTAD acknowledges that the NHAS is not a magic bullet; however, the NHAS’ central vision of the U.S. becoming “a place where new HIV infections are rare” cannot be realized until the nation aggressively responds to the core of the matter: pervasive and unmitigated stigma and discrimination against people living HIV/AIDS that diminishes our best efforts to combat one of the greatest public health challenges of our time.

As a member of the Positive Justice Project, a coordinated national effort to address “HIV criminalization” statutes – laws that create HIV-specific crimes or which increase penalties for persons who are HIV positive and convicted of criminal offenses – NASTAD supports efforts to examine and
support level-headed, proven public health approaches that end punitive laws that single out HIV over other STDs and that impose penalties for alleged nondisclosure, exposure and transmission that are severely disproportionate to any actual resulting harm. Steps identified to reach this goal in the Federal Implementation Plan include step 3.3, Promote public health approaches to HIV prevention and care which states that “state legislatures should consider reviewing HIV-specific criminal statutes to ensure that they are consistent with current knowledge of HIV transmission and support public health approaches to screening for, preventing and treating HIV.” In addition, step 3.4, Strengthen enforcement of civil rights laws requires an examination and report by the Department of Justice on HIV-specific sentencing laws and implications for people living with HIV.

HIV criminalization has often resulted in egregious human rights violations, including harsh sentencing for behaviors that pose little to no risk of HIV transmission. Thirty-four states (34) and two (2) U.S. territories explicitly criminalize HIV exposure through sex, shared needles or, in some states, exposure to “bodily fluids” that can include saliva. Examples include:

- A man with HIV in Arkansas was sentenced to 12 years (and must register as a sex offender after release) when he failed to disclose his status with his girlfriend and another woman – both women tested negative;
- A man with HIV in Iowa, who had an undetectable viral load, was sentenced to 25 years after a one-time sexual encounter during which he used a condom;
- A woman with HIV in Georgia, who was sentenced to eight years imprisonment for failing to disclose her viral status, despite it having been published on the front page of the local newspaper and two witnesses who testified her sexual partner was aware of her HIV positive status.

In none of the cases cited was HIV transmitted. In fact, most prosecutions are not for transmission, but for the failure to disclose one’s HIV status prior to intimate contact, which in most cases comes down to competing stories about verbal consent that are nearly impossible to prove.

HIV criminalization undercuts our most basic HIV prevention and sexual health messages, and breeds ignorance, fear and discrimination against people living with HIV. NASTAD members commit to examining existing public health policies related to HIV criminalization that may exacerbate stigma and discrimination and lessen the likelihood that individuals will learn their HIV status. NASTAD members will also continue to emphasize the importance of providing comprehensive prevention and care services for HIV positive individuals to help reduce the risk of transmission to others. In conjunction with new and existing partners, our members also pledge to:

- Support the maintenance of confidentiality of HIV test and medical records in order to encourage and support individuals to be tested, learn their status and enter services if positive;
- Identify and share best practices related to successes in repeal of policies and/or laws and statutes in jurisdictions that are not grounded in public health science; Promote public education and understanding of the stigmatizing impact and negative public health consequences of criminalization statutes and prosecutions;
- Provide unequivocal public health leadership on the relative risks of transmission and the dangers of a punitive response to HIV exposure on the epidemic.

NASTAD will continue to advocate at the national level to raise awareness of this urgent issue. Realizing the vision of the NHAS is predicated on a strong foundation of public health science and practice void of stigma and discrimination. Instead of applying criminal law to HIV transmission, state and local governments should expand programs to reduce HIV transmission while protecting the human rights of people living with HIV.

Approved by NASTAD’s Executive Committee: February 2011

**Cholera Epidemic In Haiti Could Affect Twice As Many As Previously Estimated**

The cholera epidemic in post-quake Haiti could affect as many as 800,000 people and kill 11,000 by December, twice the number the U.N. estimated would be affected, according to a study published in The Lancet, National Journal reports. Jason Andrews of the Harvard School of Public Health and colleagues used data from Haiti’s Ministry of Health to predict the spread of cholera in the country, and they present a three-tiered approach to fighting the waterborne disease, which until last year’s earthquake response had not been seen in the country for a century. The researchers recommend “reducing consumption of contaminated water by 1 percent; vaccinating 10 percent of the population; and giving antibiotics to all patients with severe dehydration and to half of patients with moderate dehydration to avert 177,000 cases and 3,700 deaths,” National Journal writes.
The Pan American Health Organization, which opposed cholera vaccinations until December 2010 in part because of a lack of vaccines, said up to one million doses of cholera vaccine could become available in the second half of 2011, according to the publication (Edwards/Fung, 3/15). The WHO "says everything possible is being done to contain the disease and warns that modeling estimates can be inaccurate," BBC News reports (Roberts, 3/15). So far, the U.S. has contributed more than $45 million to cholera relief in Haiti, "with most going to maintaining sanitation, according to USAID," National Journal writes (3/15).

**Artesunate More Effective Than Quinine At Preventing Malaria Deaths, Review Shows**
The "antimalarial drug artemesunate is more effective than quinine at preventing death in patients with severe malaria," according to an updated review published by Cochrane researchers, ANI/Sify News reports (3/16). "According to the results, taking artemesunate reduces the risk of death by 39% in adults and 24% in children compared to quinine. In adults, deaths caused by severe malaria were reduced from 241 per 1,000 with quinine to 147 with artemesunate. In children, deaths were reduced from 108 per 1,000 with quinine to 83 with artemesunate," according to a press release. "There is now enough evidence to be confident of these results in adults and children," said Peter Olumese of the WHO's Global Malaria Program, according to the release. "Intravenous artemesunate is now being recommended as the treatment of choice for adults and children with severe malaria anywhere in the world," he added (3/15).

**Cash Incentives Have Potential To Prevent HIV Among Young Sub-Saharan African Women**
In sub-Saharan Africa, some young girls take payments from older men, known as "sugar daddies," in exchange for sex, a practice that exacerbates the spread of HIV and other sexually transmitted infections, Bloomberg News reports in an article examining the potential of and controversy over programs that offer cash incentives to such women so they will not feel the pressure to take such payments. One and a half years into a World Bank-led study in Malawi, infection rates among a group of women who received an average of $10 a month and school fees if they attended class "were 60 percent lower among schoolgirls who got cash: 1.2 percent, compared with 3 percent," who received no incentives, according to the news service (Clark, 3/15).

**Breaking the mucus barrier unveils cancer cell secrets**
Washington, D.C. (March 16, 2011) — Measuring the mechanical strength of cancer cell mucus layers provides clues about better ways to treat cancer, and also suggests why some cancer cells are more resistant to drugs than others, according to Kai-tak Wan, associate professor of engineering at Northeastern University, Boston, Mass.

According to Wan, healthy tissues naturally secrete mucus to protect against infection. Cancer cells, however, produce far more mucus than healthy cells.

Mucus consists of protein "stalks" attached to sugar sidechains, or "branches." This tangled brush forms a physical barrier. When over-expressed, it can prevent drugs from reaching the cancer cells beneath. Over-expressed mucus also makes it easier for cancer cells to break away from surrounding cells and move through the body, or metastasize.

Wan's research partner, Robert B. Campbell, an associate professor of pharmaceutical sciences at Massachusetts College of Pharmacy and Health Sciences, Worcester, Mass., is investigating the use of chemical agents that limit the formation of this tangled mucus barrier so medicines can get through.

To determine how well those agents work, Wan used the nanoscale tip of an atomic force microscope to push against the mucus barrier. The less resistance it encountered, the less tangled the barrier.

Wan found that suppressing the formation of mucus sidechains significantly reduced the energy needed to pierce the mucus barrier in lung, breast, colorectal, pancreatic, and wild type (natural) ovarian cancer cells.

Yet the treatment registered barely any change in multi-drug resistant ovarian cancer cells. No one understands how those cells resist drugs that ordinarily kill wild type ovarian cancer.

Wan's research points to an important difference. The mucus layer formed by the two types of cells reacts differently to the same chemical treatment.

"How this phenomenon is related to biochemistry is unknown at this stage, but it tells us what we should be looking at in future research," Wan said about his and Campbell's conclusions.
The article, "Glycoprotein mucin molecular brush on cancer cell surface acting as mechanical barrier against drug delivery" by Xin Wang, Aalok A. Shah, Robert B. Campbell, and Kai-tak Wan appears in the journal Applied Physics Letters. See: http://link.aip.org/link/applab/v97/i26/p263703/s1

March 16, 2011, 5:38 PM ET

**In New York, A Rare Case of HIV Transmission From a Live Organ Donor**

The New York State Department of Health alerted hospitals and transplant centers Tuesday that an organ recipient recently contracted the virus that causes AIDS from a live kidney donor in an unnamed city hospital. It's the nation's first documented case of HIV transmission via a transplant from a living donor since a sensitive test for the virus was approved and implemented for donor screening in 1985, according to the health department.

A department spokeswoman tells the Health Blog that the hospital followed acceptable protocols in an initial screening of the donor, but that he apparently had “unsafe sex” after the test and prior to donating the organ. “Of course this is a rare case, but we felt like we needed to alert centers to this possibility so they can talk to potential donors about risks and do testing closer to the time of surgery,” she says.

The state declined to name the hospital in the interest of protecting the privacy of the patient.

The department is now recommending that hospitals test donors for HIV and the hepatitis C and B viruses within 14 days before the organ donation, using nucleic acid testing. NAT can detect viral infections weeks to months before antibodies are detectable by standard serologic tests. It hasn’t been recommended for testing organs from deceased donors because of the time pressure of transplanting the organs before they deteriorate, but that time crunch shouldn’t apply to potential living donors, the state notes in its advisory.

Testing for infectious disease has all but eliminated the transmission of HIV through organ, tissue and blood donation. The Centers for Disease Control and Prevention last issued HIV-specific organ-donation screening recommendations in 1994 and is expected to update its recommendation this year.

The state is advising hospitals to question living organ donors about risky behavior, including the use of non-medical injectable drugs. Compliance with the specific recommendation is voluntary but the department is urging all centers to update their policies for screening living donors as necessary.

The transplant community’s [most recent testing recommendations](http://link.aip.org/link/applab/v97/i26/p263703/s1), which appeared in the American Journal of Transplantation last year, said that average-risk donors do not require NAT screening; they didn’t address the timing of screening. The health department says it doesn’t believe those recommendations are sufficiently protective because of the challenges of detecting behavioral risks and learning about the infection status of a donor’s sexual partners.

**Rwanda: UNAIDS Chief Commends New Circumcision Device**

Edwin Musoni
17 March 2011

The visiting Executive Director of UNAIDS, Michel Sidibé, said that Rwanda’s new male circumcision device, the PrePex system—signals a major revolution in the global fight against HIV.

Sidibé, who also doubles as the Under Secretary-General of the United Nations, made the remarks after witnessing how the device is used during his visit to Nyamata Hospital.

"What I have witnessed today marks a revolution in terms of circumcision. This is simple technology that can be rolled out to the entire world," Sidibé said.

The PrePex System, a new device and methodology for rapid adult male circumcision, works through a special elastic mechanism that fits closely around an inner ring, trapping the foreskin, which dries up and is removed after a week.

The system does not need a sterile environment or anaesthetic, and men can be back at work within a short time, rather than taking several days to heal. "It takes only two minutes to conduct circumcision using this system meaning it is time saving, there is no pain to the patient, and it contributes to the reduction of HIV contraction by 66%," Sidibé added.

He, however, noted that there is need to link the scientific evidence and cultural change to stem new HIV infections.

The Permanent Secretary in the Ministry of Health, Dr. Agnes Binagwaho, said that her ministry is proud to be behind the groundbreaking research which is likely to change the world. Binagwaho is one of the researchers on the new system.
"The most interesting thing about this system is that, it doesn’t require going to the theatre, it can be done from any clean environment. It is also cost-effective and eliminates factors such as anaesthetic and highly trained staff. Any well-trained person can conduct it," Binagwaho said.

According to Dr. Leo Ngeruka, research on the system is still on-going and volunteers are above the 21 years. In a related development, a ten-man delegation from Zimbabwe also visited Nyamata Hospital to witness how the PrePex System works.

Several African countries have expressed interest in the system.

**Female condoms are gaining ground**

**By Rita Rubin, USA TODAY**

The female condom, once the contraceptive that got little respect, seems to be making a comeback in U.S. cities, thanks to a new and improved design.

The Food and Drug Administration approved the first female condom in 1993.

On Valentine’s Day, San Francisco’s health department passed out free FC2s — short for second-generation female condom — in several neighborhoods.

That same week, Walgreens stocked about 10% of its 7,600 stores — many in cities with higher HIV rates — with three-packs.

And in Washington, where all 55 CVS stores carry it, 25,000 people used it in the past year, says Mary Ann Leeper, founder of its maker, the Female Health Co. In fact, she says, the number of FC2s distributed in the USA tripled in the past year. It’s the only female condom on the U.S. market, but it’s sold in more than 100 other countries and even has a Facebook fan page.

Health departments in Chicago, New York City and New York state also have joined with non-profit groups to distribute the female condom not only to women but also to gay men, even though evidence about its safety and effectiveness in anal sex is lacking.

The Food and Drug Administration approved the first female condom in 1993. Hundreds of Walgreens stocked it, but it was hard to find elsewhere and it cost more than male condoms. But it was an effective, woman-controlled method to prevent pregnancy and the spread of sexually transmitted infections. The FDA approved the FC2 in March 2009.

FC1 was made of polyurethane, Leeper says; FC2 is made of easier-to-work-with synthetic latex.


Another plus, says Jessica Terlikowski, policy manager of the AIDS Foundation of Chicago: "There are no seams, so it’s more comfortable to wear."

**Cholera Vaccines Can Prevent Up To 60% Of Cases In First Two Years Following Vaccination**

Currently available cholera vaccines can prevent up to 60 percent of cholera episodes during the first two years following vaccination, according to a review published in the Cochrane Library on Wednesday, ANI/Sify News reports. The authors analyzed "40 studies that examined the effect of cholera vaccinations incorporated into a routine vaccination schedule in areas of the world where the disease is prevalent," according to the news service (3/16). They note, "The impact and cost-effectiveness of adopting oral cholera vaccines into the routine vaccination schedule of endemic countries will depend on the prevalence of cholera, the frequency of epidemics, and access to basic services providing rapid rehydration therapy" (Sinclair et al., 3/16).

**Why Are the Elderly So Vulnerable to Pneumonia?**

ScienceDaily (Mar. 11, 2011) — A study featured on the cover of the March 15 Journal of Immunology is providing insight into why the elderly are so vulnerable to pneumonia and other bacterial infections.

Compared with younger adults, the elderly are at higher risk of becoming seriously ill or dying from pneumonia. Moreover, vaccines against the disease are less effective in the elderly.

To help understand why, Loyola researchers examined two types of immune system cells, macrophages and B cells, located in specialized areas in the spleens of mice. (Macrophages gobble up bacteria, while B cells produce antibodies that fight bacteria.)

Macrophages and B cells appeared to be just as effective in old mice as they were in younger mice. But there were fewer of them.
"If we knew how to replenish these cells, we might be able to lower the risk of bacterial infections in the elderly," said senior author Pamela Witte, a professor in the Department of Microbiology and Immunology at Loyola University Chicago Stritch School of Medicine. "This is an unexplored area in aging."

The finding also could provide clues to developing vaccines against pneumococcal pneumonia that would be more effective in the elderly, said first author Shirin Birjandi, who is completing her PhD at Loyola.

For example, Birjandi said, current vaccines instruct B cells to make antibodies against bacteria that cause pneumonia. But if humans are like mice, the elderly will have fewer B cells. So it might make more sense to develop vaccines that instead target other immune system cells, Birjandi said.

In their study, Loyola researchers examined B cells and macrophages that form microscopic rings in the spleen called marginal zones. These marginal zones form protective rings, preventing bacteria from passing through.

Photographs taken by the researchers show that in the spleens of young mice, macrophages form distinct rings in the marginal zones. (One of these photos appears on the cover of the Journal of Immunology.) In old mice, however, the photographs show that marginal zone rings are dramatically disrupted. (In humans, the equivalent ages of the old mice would be between 70 and 80.)

Researchers wrote that understanding changes such as these "is important for developing more efficient therapies for preventing diseases, such as bacterial pneumonia, that have shown to be highly detrimental in the elderly."

Journal Reference:

**Developing a Universal Flu Vaccine?**

ScienceDaily (Mar. 16, 2011) — A vaccine that helps against all types of influenza—for several years? If all goes right for Norwegian company Bionor Pharma ASA, such a vaccine could exist within a few years.

Every year, experts develop a new vaccine to best combat the coming annual flu wave, based on the previous year's virus and others expected to arrive. Developing a vaccine that meets its mark, however, is a true challenge.

The year 2010 presented major challenges because scientists have only limited experience in dealing with flu seasons following a pandemic such as the outbreak of swine flu in many countries in 2009. The complexity of flu transmission in the Southern Hemisphere compounds the difficulty of predicting which virus will emerge as the most predominant in, say, Norway.

The vaccine that Bionor Pharma's scientists are developing will be less dependent on which form the various flu viruses take.

**Triggers immune cells**

"Vaccines for seasonal flu consist of virus particles based on the virus that is expected to predominate," explains Maja Sommerfelt, Chief Scientific Officer at Bionor Pharma. "But the vaccine we are developing uses only the particles that are common to all type-A flu viruses, in people as well as animals." Dr Sommerfelt heads a flu project that receives funding under the National Programme for Research in Functional Genomics in Norway (FUGE), one of the Research Council's Large-scale Programmes.

In this way, the vaccine will provide basic immunity to all of the most common flu viruses. It is also expected to have a long "memory" so that people do not need a new vaccination each year.

The vaccine will also work in a different way from other flu vaccines. Typical seasonal flu vaccines block the virus by triggering an antibody response. Bionor Pharma's vaccine, however, allows the virus to invade the cells, which are then quickly destroyed by the immune system—preventing the virus from spreading.

"So we may become infected," says Dr Sommerfelt, "but the vaccine triggers our immune cells, which quickly seek out and kill the infected cells. The virus factories are removed, so to speak, preventing the illness from spreading throughout our body. We don't become as ill as we otherwise would."

She believes the vaccine will save lives and yield positive social and economic benefits. Fewer people will have to stay home from work to recover—or to tend to their infected children.

**Inspired by HIV vaccine**

The idea for a new kind of flu vaccine arose in connection with the company's research on an HIV vaccine.
"Like the flu virus, HIV is a highly variable virus, appearing in many forms. Amidst all the concerns about a flu pandemic during the 2005-2006 outbreak of avian influenza," recalls Dr Sommerfelt, "it occurred to us that the flu virus may be a good candidate for the type of vaccine we were developing for HIV."

Viruses contain proteins, and both the HIV and flu vaccines that Bionor Pharma is developing are based on tiny protein fragments called peptides. When a cell becomes infected, it expresses these peptides outside the cell, which alerts the immune cells to come and destroy that cell.

The genetic composition of every known flu virus worldwide is stored in databases, including information about the various viral proteins.

"We analysed amino acid sequences in all the proteins to determine the areas they share in common," continues Dr Sommerfelt. "Next we researched how we could alter these sequences so that they would stimulate the immune system in the greatest proportion of the population."

**Several years to go**

She believes a universal flu vaccine will also help to prevent pandemics, which occur when a completely new flu virus emerges that is highly contagious and resistant, spreading rapidly across the globe.

"If an entirely novel virus should emerge, it would take a long time to develop a pandemic vaccine. Fortunately, last year's swine flu did not take the serious turn that was feared. Had that outbreak been more powerful, though, it would've been nice to have a peptide vaccine to provide some basic immunity."

Dr Sommerfelt stresses that much remains to be done before we can go to the doctor for a peptide flu vaccine that will remain effective for several years or seasons. Vaccines must undergo three lengthy clinical testing phases. She and her colleagues are also investigating other, non-injection-based ways of administering the vaccine, with an eye to mass immunisation.

"It will take at least seven to eight years before we have a vaccine on the market," says Dr Sommerfelt. In the meantime, we can only hope that the human immune system can tackle the viruses on its own, or cross our fingers that this year's seasonal flu vaccine hits the bull's eye.

**Improving the Infant Gut 'microbiome'**

ScienceDaily (Mar. 16, 2011) — While next-generation sequencing-based research of gut microbiomes will ultimately benefit all members of the population, to date there has been a particular emphasis on investigating and, where necessary, altering the microbiota present in the gut of the elderly, infants and obese individuals. For example, evidence exists that early colonization of the infant gastrointestinal tract by microbes is crucial for the overall health of the infant.

Sequencing technology has advanced significantly since the race to sequence the human genome first began. As part of the Teagasc Vision Programme a 'next generation sequencer', the only one of its kind in Ireland, was installed at Teagasc Food Research Centre, Moorepark.

This technology is being used to sequence microorganisms from one of the most extreme environments, i.e., the human gastrointestinal tract (gut). The human gut has the potential to impact hugely on the health of individuals. This is because microbes correspond to nine out of every ten cells in our body. Indeed, in the large intestine the number of microbes can be as high as 100 billion per gram. This collection of microbes is known as the human 'microbiome'. This microbiome contains 100 times more unique genes than those present in our own genomes, and has a metabolic capability equivalent to that of our liver.

"While everybody is aware that there are a number of gut microbes that can make us sick, the majority of gut microbes are harmless and, indeed, a significant number can have a positive impact on our health. It has only been since the advent of next-generation sequencing technologies that we have been able to properly appreciate what microbes are present in the gut and what they might be doing," explains Dr Paul Cotter in an article in TResearch, Teagasc’s Science magazine.

These roles include vitamin synthesis, the digestion and absorption of foods, immunostimulation, the control of disease-causing microbes (pathogens) and prevention of other diseases, human intestinal cell proliferation, and aiding bowel movements. Now, armed with this knowledge, researchers at Teagasc can add considerably to the health claims, and thus value, associated with existing foods, and design the next generation of functional foods by identifying ingredients that impact positively on the composition of our gut microbiome and, in turn, our health.

While next-generation sequencing-based research of gut microbiomes will ultimately benefit all members of the population, to date there has been a particular emphasis at Teagasc on investigating and, where necessary, altering the microbiota present in the gut of the elderly, infants and obese individuals.
For example, evidence exists that early colonisation of the infant gastrointestinal tract by microbes is crucial for the overall health of the infant.

"The infant microbiota is influenced by factors such as the mode of delivery, the maternal microbiota, antibiotic exposure and other factors. Significantly, one of the major influencing factors is whether the infant is fed breast milk or infant milk formula. Breast milk is the ideal food for infants and contains a number of components that promote a healthy gut microbiota. Thus, producers of infant milk formula would like to generate new and improved formulae that more closely resemble breast milk with respect to its impact on the infant gut microbiota," explains Dr Cotter.

Comparison of Wiping Away Bacteria With Disinfectant Wipes or a Tissue Moistened With Saline

ScienceDaily (Mar. 17, 2011) — If you have time to quickly swipe your pager or cell phone three times, that would be your best bet to get rid of most of the bacteria. And a simple tissue moistened with saline would do the trick. But if you only have time for a single swipe of a 'dirty' phone—you’d be better off reaching for a disinfectant wipe.

Those are the highlights of a recently published research study that appeared online in PubMed, with the discoveries having been made by a team of researchers in the Faculty of Medicine & Dentistry at the University of Alberta. "It was the mechanical removal, not the actual act of the disinfectant that was key," says Dr. Sarah Forgie, a Pediatric Infectious Diseases Specialist in the Department of Pediatrics.

Medical student Andrea Berendt, who was working with Forgie at the time, liked the idea so Berendt came up with the protocol and conducted all the experiments in a lab over two months. The duo worked with Dr. Robert Rennie, a Professor in Laboratory Medicine and Pathology, Pediatric Epidemiologist Donald Spady and technologist LeeAnn Turnbull.

Three types of bacteria—Staphylococcus aureus (MRSA), Enterococci (VRE) and Pseudomonas aeruginosa—were each prepared in a mixture and streaked onto sterile plastic Petri dishes, then allowed to dry. Numerous bacteria contaminated plates were prepared throughout the summer—all in the same manner—so each type of bacteria could be tested with five different types of wipes and then again with varying amounts of swipes—one swipe, three swipes and five swipes.

Each 10 cm diameter plate was wiped for one second and in a manner that the entire surface was swiped, using a flat baton. The plates were then allowed to dry for 10 minutes. Afterwards, bacteria samples were put onto special lab plates, incubated for at least 24 hours at 35 degrees C and then the bacteria colonies were counted.

Research results demonstrated that bacterial counts dropped significantly the more often a plate was swiped—regardless of the type of wipe used. Swiping the contaminated plates 3x decreased the bacterial load by 88% on average, compared to just swiping a plate once. Swiping a plate 5x vs. 3x didn't result in an additionally significant decrease in bacteria. And a simple saline wipe appeared to be just as effective as disinfectant wipes when the plates were swiped 3x or more. However, if the plate was swiped just once—disinfectant wipes were better at reducing bacteria than simple saline wipes.

Journal Reference:
Berendt AE, Turnbull L, Spady D, Rennie R, Forgie SE. Three swipes and you're out: How many swipes are needed to decontaminate plastic with disposable wipes? Am J Infect Control., 2011 Feb 8. [link]

Saint Patrick Didn’t Have It Easy ... but At Least the Food Wasn’t Bad

ScienceDaily (Mar. 15, 2011) — Shipped to Ireland as a slave, it must have been a cold, hungry journey for Patrick. But through her researches, Irish food expert Regina Sexton from University College Cork, has been able to recreate the diet available in 5th century Ireland to a young saint-in-the-making.

It is safe to say that obesity was not a problem in those days, and that the fare was seasonal, wholesome and modest by today's standards. Dairy produce and cereals were everyday staples and St Patrick would have consumed lots of fresh milk, sour milk, thickened milk, colostrum, curds, flavoured curd mixtures, butter and soft and hard cheeses.

Cereals, most commonly oats and barley, a little rye together with more prestigious and high-ranking wheat, were used in the production of flat breads and it is also likely that leavened wheat loaves were on offer. Various wet preparations such as porridge, gruel, meal pastes and pottages as well as cereal-milk and fruit-nut combinations were also being eaten on the island when the young Patrick arrived. A wide range of wild foods, notably watercress and wild garlic, nature's way of garnishing the delights of the
countryside, was also on the menu, and if this didn't whet his appetite, there were hen and goose eggs, honey, fish, butter, curds, seaweeds, apples and dairy as well as several varieties of soft and hard cheeses.

The rivers were flush with salmon, trout and eel, and hard-cured pork as well as other meats, were to be had too. This was neither a throw-away nor a take-away society and people took good care to preserve and conserve for future use, foods that could not be consumed immediately. Much of this is known, according to Sexton, because with the coming of Christianity, monastic settlements encouraged learning and record keeping and those records have come down to us. Ironically, much of the food available then, is what we call 'health food' now, which comes of course, at a premium price.

Little wonder then that even after his daring escape from Ireland, Patrick returned to become the island's patron saint. He did it for the good of his health!

**Transmissible treatment proposed for HIV could target superspreaders to curb epidemic**

Engineered, virus-like particles would hitch a ride with HIV to reach high-risk populations that don't seek or comply with medical treatment and are responsible for a disproportionate share of disease, a new model demonstrates

Biochemist Leor Weinberger and colleagues at the University of California, San Diego and UCLA have proposed a fundamentally new intervention for the HIV/AIDS epidemic based on engineered, virus-like particles that could subdue HIV infection within individual patients and spread to high-risk populations that are difficult for public health workers to reach.

With a model that considers the effects of the proposed treatment on several scales, from interference with HIV in infected cells to viral loads in individual patients to the prevalence of HIV in large populations, they determined that the engineered particles could work in concert with current treatments for HIV infection and lower the prevalence of infection more effectively than current drugs or proposed vaccines alone. Their findings will appear in the March 17 issue of *PLoS Computational Biology*.

"Dr. Weinberger's idea to use engineered virus-derived particles to combat infectious diseases is truly provocative," said James Anderson, M.D., Ph.D., Director of the Division of Program Coordination, Planning, and Strategic Initiatives. Anderson oversees the NIH Common Fund, which supports a series of exceptionally high impact, trans-NIH programs including the NIH Director's New Innovator Award, which Weinberger received in 2009.

The engineered particles, called therapeutic interfering particles or TIPs, would persist for years in an individual patient and could be packed with genes that disrupt the functioning of HIV. Weinberger's team has succeeded in creating functional prototypes in the lab.

"TIPs are molecular parasites that 'piggyback' on HIV to spread between individuals," Weinberger said. The engineered particles use the same outer envelope as HIV but lack the genes for components of this structure and the enzymes needed to assemble it. They can only replicate, infect additional cells and transmit to new individuals by stealing these elements from HIV. Until the host cell is infected with HIV, TIPs remain dormant.

In an HIV-infected individual, TIPs would transmit to others in the same ways as the natural virus – through unprotected sex or shared needles, for example. That means TIPs would, by design, penetrate high-risk populations that are responsible for a disproportionate share of the spread of disease and can be particularly difficult for public-health officials to reach.

Using an epidemiological model, Weinberger and colleagues compared the predicted effects of the treatment they propose with current drug campaigns and hypothetical vaccines and found that TIPs could be more effective.

An intervention using TIPs could lower the number of people infected with HIV in sub-Saharan Africa to one thirtieth the current level in about 30 years, they found. Optimistic predictions for vaccine campaigns or currently available antiretroviral therapy would lower the number of HIV-infected people by less than one half the current level over the same period of time.

TIPs wouldn't replace other therapies, Weinberger said, "In part, we are arguing that TIPs could be used in conjunction with current antiretroviral drug therapy or vaccine campaigns, and could enhance the efficacy of these campaigns at the population level."

Weinberger acknowledges that an infectious treatment raises ethical concerns and is working with bioethicists to explore the unique issues associated with any use of TIPs in more detail.

He also points out that vaccines already in use can spread from one person to another. People who receive the oral polio vaccine, for example, "shed" the weakened version of the virus that is the basis of the
vaccine and this can transmit immunity to other individuals. Public health officials see this transmission as a benefit; it is one reason why this form of polio vaccine was chosen for the worldwide effort to eradicate the disease.

**Transplant Patient Got AIDS from New Kidney**

*Associated Press*, (03.17.2011)


Neither the donor nor the recipient knew he or she was HIV-infected until approximately one year after the transplant surgery. The recipient’s multiple hospitalizations were initially thought to be organ rejection. Then the patient was treated for oral and esophageal candidiasis, and HIV testing indicated a positive result. The recipient’s CD4 cell count was found to be under 100. Also about one year post-transplant, the donor sought repeat STD testing with his primary care provider and learned he was HIV-positive. The transplant team became aware of his diagnosis during a one-year follow-up visit.

The donor had reported a previous syphilis diagnosis and a history of male sex partners in his initial transplant evaluation. Testing 79 days before the procedure showed no evidence of HIV, hepatitis B or C infection. However, the investigation revealed he had had unprotected sex with one male partner of unknown HIV status during the one year before the transplant, including the time between his initial evaluation and surgery for organ harvesting.

To prevent and screen for HIV in prospective living organ donors, CDC is recommending the following:

- All living donor candidates should have their initial serologic HIV tests confirmed with a combination of an HIV serologic test and nucleic acid testing as close to organ donation as possible, but no longer than seven days prior.
- All living donors should be counseled on avoiding risky behaviors before transplant surgery.
- Living donors with a history of high-risk behaviors should be given individualized counseling and provided with specific strategies to avoid these behaviors.
- Transplant recipients should be advised of the risk for HIV and other pathogens—consistent with current policy—since no available testing can completely eliminate these risks.

Increasingly, kidney transplants involve live donors—from 32 percent of transplant surgeries in 1988 to 46 percent last year. Roughly 88,000 people are currently on the kidney waiting list, according to the United Network for Organ Sharing.


**Nevirapine for breastfeeding infants: benefit of 6-week course still evident after one year**

Carole Leach-Lemens
Published: 18 March 2011

Use of six weeks of extended-dose nevirapine compared to single-dose nevirapine accounted for a 62% reduction in infant mortality and a 46% reduction of HIV transmission or death in breastfed, HIV-exposed infants, according to the final 12-month analysis of the SWEN study.

Saad B. Omer and colleagues reported the final analysis of the Six Week Extended Dose Nevirapine (SWEN) randomised controlled trials in the advance online edition of *AIDS*.

These results confirm earlier reported analyses of six-week and six-month endpoints of the three SWEN trials.

The reduction in risk was only seen in infants born to mothers with CD4 counts above 350 cells/mm³.

Among infants of women with baseline CD4 cell counts below 350 there were no significant differences between single-dose and extended-dose nevirapine in infant death, HIV transmission, and HIV transmission or death.

Evidence of nevirapine resistance, as with other studies, was found in infants infected by six weeks of age: in the Ugandan part of the study 50% of infants who got single-dose nevirapine developed resistance compared to 84% of those who received extended-dose nevirapine prophylaxis. Similarly in India prevalence was 38% and 92%, respectively.

So recent evidence of the effectiveness of starting ART in infants under 12 weeks of age raises the concern of what regimen to use in infected infants who got extended dose nevirapine, note the authors.
They add, the increased risk for nevirapine resistance following extended dose nevirapine prophylaxis must be considered “against the benefit in the prevention of HIV transmission and death in breastfeeding infants of HIV-infected mothers.”

In resource-poor settings mother-to-child transmission of HIV continues to be a major cause of death and disease. Breastfeeding accounts for about a third of the estimated more than 420,000 children infected each year.

Because of the increased risks of death and disease from not breastfeeding compared to the risks of HIV-transmission, the World Health Organization (WHO) recommends that national authorities make a decision to recommend breastfeeding or not, based on local capacity to implement safe formula feeding.

Since safe and affordable replacement options to breastfeeding are severely limited in most resource-poor settings, effective strategies to prevent transmission through breastfeeding are critical.

Maternal ART, when available, can be protective against transmission. Lower maternal CD4 cell counts are associated with a greater probability of MTCT and death. And many women in resource-poor settings present late for antenatal care. For ART to be effective in PMTCT viral loads need to be undetectable. This can take several weeks. Maternal and infant single-dose and infant extended-dose nevirapine offer important alternative means of protection for the infants of HIV-infected breastfeeding mothers.

Infants in Ethiopia, India and Uganda born to HIV-infected mothers were randomised to get single-dose or extended-dose nevirapine. A total of 2067 HIV-positive mothers gave birth to 2037 infants at the three sites.

An analysis of 1890 infants with 987 in the single-dose nevirapine group and 903 in the extended-dose nevirapine group was undertaken. Information about the endpoint status at 12 months was available for 902 (91.3%) and 803 (88.9%), respectively.

Enrolment began in February 2001, August 2002 and July 2004 in Ethiopia, India and Uganda, respectively and the last 12-month follow-up in the respective countries was April 2007, September 2007 and July 2007.

While HIV transmission in the extended-dose group was 8.9% compared to 10.4% in the single-dose group, the difference was not significant (risk ratio: 0.87, 95% CI: 0.65-1.15).

At 12 months there was significant lower cumulative death (close to half) in the extended-dose group compared to the single-dose group (risk ratio 0.53, 95% C: 0.32-0.85), most notably in infants who were uninfected by six weeks of age.

However, only in infants born to mothers with CD4 cell counts over 350 cells/mm³ were risk ratios for death (RR:0.38, 95% CI: 0.17-0.84) and for HIV transmission or death (RR: 0.54, 95% CI: 0.35-0.85) statistically significant among those who received extended-dose nevirapine.

These findings have clinical and policy implications for exposed but uninfected infants, note the authors.

Unable to account for the higher number of HIV-infected infants at birth in Uganda, the authors suggest this is perhaps due to chance. It may have contributed to an underestimation of the reduction in HIV infection and HIV infection or death.

The authors conclude where access to antiretrovirals is limited and safe replacement feeding is not an option these findings together with results from the PEPI and BAN trials “provide evidence for the use of extended-dose regimens to increase the likelihood of HIV-free survival in infants of HIV-infected breastfeeding women with CD4 cell counts over 350 cells/mm³ [that is not eligible for ART]”.

It is important to note that since the SWEN study was completed a trial comparing 6 months of nevirapine prophylaxis to the 6-week regimen used in the SWEN study has found that the longer course of prophylaxis significantly reduces the risk of HIV transmission from mother to child in the infants of mothers not eligible for antiretroviral treatment for their own health (CD4 counts > 350 cells/mm³)(see report).

Reference
Gut bugs to lungs' rescue

Commensal microbes in the gut may help combat the flu virus in the lungs

[Published 14th March 2011 07:00 PM GMT]

The commensal bacteria of the gut, essential for digestion and the overall well-being of the intestines, also play a critical role in mounting an immune response to the flu virus in the lungs.

The results, published today (March 14) in the Proceedings of the National Academy of Sciences, suggest that antibiotic use could impair a person's ability to combat the seasonal virus.

"This work is in line with an emergence of research about how much commensal [bacteria] affect not only the metabolism of a host, but also the immunity," said Yasmine Belkaid, chief of the Mucosal Immunology Section at the National Institute of Allergy and Infectious Diseases. "It's a very informative study."

A team at the Yale University School of Medicine treated mice with combinations of antibiotics, then challenged them with the influenza virus. The animals exhibited a significantly impaired immune response, including reduced levels of T cells and influenza-specific antibodies, and high amounts of virus in the lungs.

"This was a finding that we didn’t expect," said senior author Akiko Iwasaki, an immunologist at Yale. The study is the first to demonstrate that commensal bacteria provide a signal to the body that prepares distal organs, in this case the lungs, to mount an immune response, she said. "It seems that the commensal bacteria in the gut are providing a crucial signal throughout the body that prepares the body for fighting infection," said Iwasaki.

The specific mechanism by which the microbes help mount an immune response is unclear, though the researchers suspect a role for the secretion of cytokines, which activate immune cells. In the antibiotic treated mice, these cytokines were not being synthesized in the lungs, as they were in untreated mice. It's possible, they say, that the microbes activate Toll-like receptors in the gut — important receptors for immunity—and lead to the release of cytokines such as IL-1beta, throughout the body.

"We think it's a distal control," said Iwasaki. "Something that's happening in the intestine is affecting the responses in other places. And it's probably not only restricted to lungs." Recent studies have linked gut microbe compositions to brain development and conditions like diabetes and obesity.

The team also has yet to determine which microbes support immune activation in the lungs, though it is most likely a neomycin-sensitive bacteria, as treating with the antibiotic neomycin alone had the same effects as an antibiotic cocktail.

The results suggest that long-term use of antibiotics could hamper an individual's ability to fight influenza, said Iwasaki, perhaps even impair the effect of a vaccine. "This is something people need to consider when they think about utilizing antibiotic treatment," agreed Belkaid. But on a positive note, the authors also suggest that probiotic treatments, such as yogurt, may help stimulate the immune system during flu season.


By Richard P. Grant

Bitter Pill

The paper


The finding

Stephen Liggett and colleagues at the University of Maryland School of Medicine set out to identify the G-protein coupled receptors (GPCRs) involved in the contraction of bronchial airway muscles that can lead to asthma. They discovered bitter taste receptors — previously only found on the tongue — on airway smooth muscle (ASM) cells, and showed that their activation causes bronchial relaxation instead.

The surprise

Liggett thought these receptors might protect against inhaled toxic substances. When his lab treated ASM cells with bitter-tasting compounds, such as saccharin or chloroquine, they saw an increase in intracellular calcium concentration — a hallmark of smooth muscle contraction, and thus presumably of bronchoconstriction. "We were thinking we’d found the cause of occupational asthma," Liggett says.
Surprisingly, when they tested the bitter substances on surgical tissue explants, they saw the muscles relax.

The relaxation
The bitter-tasting molecules very rapidly activated highly localized stores of calcium, rather than the slower, cell-wide calcium release that causes constriction. The team repeated the test in live mice, and saw the same result. “It was like nothing we had ever seen before,” Liggett says.

The drugs
There are “10,000 or more” known activators of bitter taste receptors, some of which are already used in medicine. The only issue would be making them more palatable, but that doesn’t bother Liggett much. “We’ve got more compounds than we can study,” he says.

By Tim Birkhead

The Birds and the Bees
A recent book exposes what Darwin got wrong about sexual behavior in birds, and what his error tells us about the evolution of scientific knowledge

For more than 100 years, it was widely assumed that the majority of female birds were sexually monogamous. Charles Darwin himself seems to have started that little rumor. In 1871’s The Descent of Man, he is quite explicit: “The female, though comparatively passive, generally exerts some choice and accepts one male in preference to others.” Darwin was equally clear about the behavior of male birds: they were, like human males, often promiscuous.

Darwin’s ideas were so influential that for the ensuing century, the notion of female fidelity remained unchallenged. My 2008 book, The Wisdom of Birds, out in paperback this month, tells the story of how ornithologists eventually overcame Darwin’s assumption, along with other lessons we’ve learned from studying birds. It’s likely Darwin knew it wasn’t true. He kept pigeons, and it was well known among pigeon fanciers that the birds engaged in extrapair copulation. Darwin also knew about a strain of pigeons known as thief pigeons, in which the males were so attractive they could entice an already-paired female to abandon her partner and eggs and fly off with a handsomer mate. Despite being aware of these dalliances, Darwin chose to characterize female birds as monogamous.

He was probably playing it safe. In Victorian England it simply wasn’t appropriate for a well-respected gentleman scientist to draw attention to the existence of female promiscuity, let alone to justify it in biological terms.

But Darwin wasn’t just bowing to pressure from contemporary society. His daughter Etty helped check proofs of his books and also acted as her father’s censor, striking out what she considered inappropriate passages. When Darwin did have to discuss topics he didn’t want Etty to read about, such as the sexual swellings of female primates, he wrote the section in Latin, which she couldn’t translate. When it came to female promiscuity, he took the easy way out and ignored it.

In the mid-1960s, David Lack, arguably the most influential ornithologist of the 20th century, conducted a wide-ranging survey of the mating systems of birds and “confirmed” that, more than 90 percent of all bird species breed as pairs. His implicit assumption, following Darwin, was that monogamy meant female fidelity.

By the time Lack’s results were published, more ornithologists were conducting behavioral studies of birds banded with colored rings, enabling researchers to recognize them as individuals. They noticed that
females were not always sexually monogamous. Such was Darwin’s reach that researchers explained away these anomalous results by blaming the males and assuming that they had hormone imbalances!

Then in the early 1970s, evolutionary biologists started to switch from thinking that natural selection favored or disfavored groups or populations, to focusing explicitly on individuals. Individual-selection thinking changed everything. Under the group-selection paradigm, reproduction was a cooperative venture between males and females. Under the individual-selection paradigm, however, each individual was out to maximize its own fitness.

Confirmation of widespread female (and male) promiscuity among otherwise socially monogamous birds came from detailed behavioral observations and, beginning in the mid-1980s, paternity studies using the new, extremely powerful method of DNA fingerprinting.

The results are startling. Almost every bird species previously assumed to be faithful exhibits some degree of infidelity. Certainly, there are a few truly monogamous birds, such as the mute swan, but in most species some females have some of their eggs fertilized by males other than their partner. In species like the European reed bunting, despite the maintenance of a monogamous pair bond, more than 75 percent of all eggs are fertilized by other males’ sperm.

The benefit of promiscuity for males is clear—more offspring. But what do females gain from being unfaithful? Despite 25 years of research, and paternity studies of some 150 species, we still do not know the answer. It may be that just as with the shift in evolutionary thinking in the early 1970s, another paradigm shift in our thinking is required to answer this question.

**Tim Birkhead**, a Fellow of the Royal Society, is professor of zoology at the University of Sheffield, UK. His research—mainly on birds—has taken him all over the world. He has won awards for his undergraduate teaching and is committed to the public understanding of science. An excerpt of his book can be accessed here.

This is a fascinating article and I look forward to reading Dr. Birkhead’s book. As described here, I think it will be a great addition to the reading list in my evolutionary biology class.

**Mute monogamy**

by Steve Summers, [Comment posted 2011-03-18 15:13:57]

Just a note. In an unpublished Mute Swan study I did in 1988 at a lake called Lost Lagoon in Stanley Park, Vancouver, BC, submitted to the Wildfowl Trust in Slimbridge, Gloucester, England (now Wildfowl and Wetlands trust), I observed one paired female swan copulate with an unpaired male. This action was obscured from her mate by a very small ‘island’ in the fresh water lake.

During the territorial seasons this large male occupied a territory by default with another male and was always scouting for mating and independent territory opportunities.

I once observed it rediscover what was clearly a former nest site in the company of the other male upon which it immediately became aggressive to the other male. This opportunity for discovery came about because the pair which had this overgrown nesting site at the extreme edge of their territory were being disrupted by a pair of trumpeters and being worn down in the defense of their territory.

**Why we should all learn Latin**

by Richard Patrock, [Comment posted 2011-03-18 13:05:56]

It is too bad the church fathers knew Latin. Then Darwin could have written all of his books in it and bypassed the pigeon poop the religious have dumped on him ever since. Thanks for the story about his in-house censor!

**No need for a paradigm shift**

by Derek Bickerton, [Comment posted 2011-03-01 14:49:55]

I would have thought the reason for female infidelity was obvious. A bird wants to spread her betts. Suppose after all she’d made a mistake and her original mate’s offspring turned out to be duds!

The more she adulterates, the better her chances that at least some of her descendents will survive to spread her genes.

**Female promiscuity**

by Ken Hines, [Comment posted 2011-03-01 13:27:00]

Has anyone considered the genetic data concerning how many male progenitors are represented in a nest of eggs? It would stand to reason if a female bird “mated” and also “fooled around” she would enhance the likelihood of achieving pregnancy, even if mating with the most desirable male was the uppermost consideration (all of those terms being acutely anthropomorphic).

**Female Promiscuity**

by Dennis Smith, [Comment posted 2011-03-01 10:30:41]

I think that is has been shown that the evolutionary significance of promiscuity for females with males demonstrating a higher fitness (strength, plumage color, etc.) results in higher fitness for the potential offspring of the female resulting in the increased likelihood that her genes will be more successful. This success results from the fact that her offspring will be more likely to outcompete other individuals because of the traits they carry.

**MMWR Reports on Premastication of Food by Caregivers of HIV-Exposed Children**

“Premastication (i.e., chewing foods or medicines before feeding to a child) was reported recently as a route of human immunodeficiency [virus] (HIV) transmission through blood in saliva ... and has been associated with transmission of other pathogens ... . Approximately 14% of caregivers in the United States
report premastication ... ; however, the frequency of this behavior among HIV-infected caregivers is unknown. To assess the prevalence of premastication among caregivers of children being treated in pediatric HIV clinics, which include perinatally HIV-exposed children (i.e., HIV-uninfected and HIV-infected children born to an HIV-infected mother), CDC conducted a cross-sectional survey at nine such clinics in the United States during December 2009—February 2010. This report describes the results of that survey, which indicated that among primary caregivers of children aged ≥6 months, 48 (31%) of 154 reported the children received premasticated food from themselves or someone else. Approximately 37% of black caregivers reported premastication, compared with 20% of non-black caregivers (prevalence ratio [PR] = 1.8). Premastication decreased with caregiver age and was used to feed children aged 1—36 months. ...

“Although research on the risk for HIV transmission via premastication is limited, CDC recommends that HIV-infected caregivers not premasticate food for HIV-uninfected children because of the possibility of transmitting HIV to the child. Public health officials and health-care providers should continue to educate the public about the risk for disease transmission, including HIV, via premastication.”

**Poor lower-limb strength common in patients with long-term HIV infection, French study finds**

Michael Carter  
Published: 21 March 2011  
Over half of middle-aged HIV-positive patients in a large French cohort had poor lower-limb strength, French investigators report in the online edition of *AIDS*.

They warn that this could mean the patients have a higher risk of falls and recommend that assessments of lower-limb strength should be carried out as part of routine HIV care.

Problems with balance and a deterioration of muscle strength in the lower limbs (locomotor performance) are associated with ageing. Many patients with HIV are now living into older age, and the diseases of ageing are an increasingly important cause of illness and death in these individuals.

Research conducted in 2002 showed that up to 30% of HIV-positive individuals had problems with muscle strength or balance.

Investigators from the French ANRS CO3 Aquitaine Cohort wished to gain a better understanding of locomotor performance in HIV-positive patients in the modern treatment era.

They therefore designed a cross-sectional (or “snap-shot”) study involving 324 patients who received care between 2007 and 2009.

Their locomotor function was assessed using six validated tests:

- An assessment of overall balance.
- Distance walked in six minutes at an accelerated speed.
- Time to stand up from an armchair, walk three metres, turn around, walk back to chair and sit down.
- Reach test.
- Balance test.
- Five-times-sit-to-stand, an assessment of the amount of time needed to stand up from a sitting position five times. This assesses lower-limb strength.

The patients had a median age of 48, and 80% were men. They had been living with HIV for a long time, and the median period since diagnosis was almost 13 years. Consistent with this, 83% of patients were taking HIV therapy and their median CD4 cell count was 520 cells/mm³.

Over half (53%) of individuals had a poor five-times-sit-to-stand result. “The poor...performance was considerably higher in our sample than the expected frequency in the general population,” comment the researchers.

In addition, 24% of patients performed poorly on the walking assessment, 11% had poorer than expected reach, and 10% had impaired balance.

Of the 172 patients with poor sit-to-stand results, 90 also had poor result in at least one of the other assessments.

“Eighty-four percent of patients with poor six-minute-walk performance also had poor performance in the five-times-sit-to-stand test,” note the investigators.

Surprisingly, poor performance in the sit-to-stand assessment was more common in younger patients. Results showed that 64% of individuals under 50 performed poorly in this assessment compared to only 36% of patients aged over 50. This difference was highly significant (p < 0.001).
Given the high prevalence of poor performance in the stand-to-sit assessment, the investigators restricted their statistical analysis to the factors associated with this measure of lower limb strength.

Their first analysis showed that poorer performance was associated with a range of risk factors, including: younger age (p < 0.0001), female sex (p < 0.01), injecting drug use (p < 0.01), hepatitis C co-infection (p = 0.02), smoking (p < 0.01), a lower body mass index (p = 0.01), longer duration of infection with HIV (p < 0.0001), and therapy with a “d” drug (p < 0.001).

However, their final multivariate model that controlled for potential confounders showed that only body mass index (p < 0.001) and longer duration of infection with HIV (p < 0.001) were associated with poor lower-limb strength.

The effect of body mass index differed according to age. A low body mass index was associated with poor performance in younger patients. However, the opposite was true for older patients. Nevertheless, the investigators believe that in both older and younger patients the underlying reason was low muscle mass in the legs and buttocks.

Each year of infection with HIV increased the risk of poor performance by 8%.

There was some suggestion that HIV therapy that included a “d” drug was also associated with poor lower-limb strength, but this fell short of statistical significance. Nevertheless, the investigators believe that this finding “may warrant further exploration.”

“Given the high frequency of poor five-times-sit-to-stand performance...we recommend to perform [this] test in standard care,” recommend the authors, who conclude with a call for longitudinal studies “to assess the evolution of locomotor performance and the incidence of falls in the HIV-infected population.”

Reference

Rural girls cheated into marrying HIV carriers
*VietNamNet Bridge* – Women only knew that their husbands had infected them when they were pregnant.

Doctor Bui Thi Chut from the Hanoi Obstetrics Hospital told VietNamNet that she has examined thousands of pregnant women over nearly 20 years. She could not forget some special cases, including women who were cheated into marrying HIV carriers.

According to doctor Chut, most are rural women. They all knew that they were infected with HIV from their husbands when they were pregnant and had the first examination at hospital.

The youngest victim is a 17-year-old woman from Nam Dinh province. Through a matchmaker, she agreed to marry a man in Hanoi, who was young, handsome, and rich.

She got pregnant several months after the wedding. Her mother-in-law took her to the Hanoi Obstetrics Hospital for a check-up. Holding the test result in her hands, the young woman discovered that she was a HIV carrier.

She said she had sex only with her husband. When doctors asked her husband to the hospital for tests, they were shocked when the girl’s mother-in-law said: “My son has had HIV for a long time”.

79
It turned out that the mother cheated the 17-year-old girl in order to have grandchildren. “I have only one son. If he doesn’t get marry and have children, my family will be heirless,” she told doctors.

Doctor Chut said the eldest victims are only 19 years old. But it is unacceptable that these women were not shocked when they knew that they were infected with HIV.

“Because they don’t know what HIV is and whether it is dangerous or not. Some of them told me that they had heard about it and they didn’t have any reaction. They didn’t know enough about the disease to be shocked,” doctor Chut said. The patients told doctor Chut that they got married with rich men from the city to change their lives. The mothers-in-law who cheated these girls thought that it would be good for them to seek rural girls because they are poorly educated and if they find out the truth, they will accept the fate.

Doctor Chut said that pre-marriage health examinations must be legalized to avoid such cases. It is necessary along with the development of sperm banks.

If a mother is carrying HIV, her child will not be infected if she takes anti-HIV before and after delivering the child.

HIV carriers can also have healthy children using sperm filtering technique. Doctor Chut also said that the healthcare sector must do many things to improve the knowledge of diseases for the people, especially those in rural and mountainous areas.

The girls who were cheated to marry HIV carriers all live in rural villages that are not very far from Hanoi but even they didn’t know about HIV.

**Senate Adjusts Religious Aspect of Vaccine Bill**

*The Record (Bergen County, N.J.),* (03.15.2011) Elise Young

The state Senate Health, Human Services and Senior Citizens Commission is supporting a bill that would require religious exemptions for childhood vaccinations to be “bona fide.” Currently, “bona fide” language is found only in rules related to hepatitis B vaccine protocols. Sen. Loretta Weinberg (D-Teaneck) said a clarification is needed to “put all the immunizations, vaccines under one standard.”

“By adding the words ‘bona fide,’ we certainly are suggesting that you should not be using a religion just as an excuse,” said Weinberg, who chairs the committee. With its passing, the measure now goes before the Senate for consideration.

New Jersey requires immunizations against hepatitis B, diphtheria, tetanus, pertussis or whooping cough, polio, measles, mumps, rubella, Haemophilus influenza type B, varicella or chicken pox, influenza, and meningitis.

Supporters of the bill say New Jersey’s policy on vaccine exemptions would not change. State law allows parents to opt out of vaccinations by submitting a written medical or religious reason to school officials. “We are not giving to any local official any more power than they already have today,” said Weinberg.

But critics of the measure say it could prompt officials to question parents’ affiliations. Some wondered whether the “bona fide” phrase would cover those personal beliefs not connected to an organized, recognized religion. “Parents are going to be harassed and discriminated against and judged,” warned Sue Collins, co-founder of the New Jersey Coalition for Vaccine Choice.

**Board Says Doctor Admitted He Reused Biopsy Needle Guides**

*Las Vegas Review-Journal,* (03.17.2011) Paul Harasim

The Nevada State Board of Medical Examiners (BME) recently suspended a doctor for allegedly reusing needle guides during prostate and rectal biopsies. Needle guides are the plastic sheaths through which needles are directed to obtain biopsy material, and the single-use devices regularly contact blood and body fluids.

In the suspension of Dr. Michael Kaplan’s license, BME said that the doctor called for the guides to be washed between patients undergoing the invasive procedures and discarded only when they became “too bloody.” The motive behind Kaplan’s directive is not yet known. The devices cost about $10 apiece.

Kaplan acknowledged to BME and Food and Drug Administration investigators “he had reused the endocavity needle guides during biopsy procedures,” the suspension order states.

Patients who had biopsies performed by Kaplan between Dec. 20, 2010, and March 11, 2011, could be at risk of blood-borne diseases such as HIV and hepatitis C, said Dr. Lawrence Sands, chief health officer of the Southern Nevada Health District. SNHD officials will issue a formal notification once patients have
been identified and recommendations are finalized. In the meantime, affected patients should speak with their physician about their concerns, said Stephanie Bethel, a district spokesperson.

Five people are searching through patient records “to see who has to be notified,” said Doug Cooper, BME’s executive director. “We’re doing it as fast as we can so the health district can notify patients,” he said.

BME cannot divulge how the alleged practice first came to its attention, “because that source will probably be helping us with the investigation down the line,” Cooper said. To date, no cases of disease transmission have been linked to the lapse in infection control.

**South Africans with AIDS Fear New Drug Crimes**

*Agence France Presse*. (03.20.2011)

Some HIV-positive South Africans are falling victim to thieves who steal their antiretrovirals, supposedly for use in the street drug called whoonga. Yet as such thefts increase, there is little evidence to suggest the ARVs are actually used in the drug.

The topic even rated mention by President Jacob Zuma at the opening a national substance abuse conference last week. “Experts from the University of KwaZulu-Natal have found that the whoonga does not contain ARVs, but is made up of heroin mixed with rat poison and other chemicals,” he said. “Perpetuating such inaccuracies is dangerous, as it may make drug addicts steal ARVs, which would put the lives of people on treatment for HIV at risk.”

Similar findings were reported by Anwar Jeewa, director of the Durban rehabilitation center Minds Alive. He tested six samples of whoonga obtained from different parts of the city: None had any trace of ARVs.

Jeewa does not deny that some drug users may be abusing ARVs, but he sees whoonga as more of a marketing phenomenon spawned by dealers long known to cut their heroin with other substances. “A few years ago, the same drug was called ‘sugar,’” Jeewa said. “Brand names create an interest for demand.”

Santosh Basdeo, a pharmacist in Durban’s KwaMashu township, said whoonga may be “anything from a combination of ARVs to rat poison, things that you can buy over the counter at the pharmacy, things that you even have at home,” so long as it keeps “the cost of the drug as low as possible.”

Yet the perception that ARVs are an important part of whoonga continues to drive the thefts. “In the township, you see kids stealing the medication of their parents and selling it to the people who make whoonga,” said Nonhlanhla of KwaMashu, whose own ARVs were stolen.

**Studies Shed Further Light on Cardiovascular Disease among People with HIV**

**SUMMARY:** HIV positive people are at higher risk for cardiovascular disease overall, compared with HIV negative individuals, according to findings from Kaiser Permanente presented this month at the 18th Conference on Retroviruses and Opportunistic Infections (CROI 2011). Other studies found that HIV positive people on ART with well-preserved immune function were not at greater risk, however, and that abacavir (Ziagen) was not linked to heart attacks.

By Paul Dalton

As HIV treatment proves increasingly effective, at least in developed countries, attention has shifted to the long-term consequences of both HIV disease and its treatment.

The impact of HIV and antiretroviral therapy on cardiovascular health is of particular interest, as heart disease remains the biggest health issue in the U.S. This year’s CROI featured several presentations covering cardiovascular disease and HIV.

**HIV and MI Risk**

Evidence from the SMART treatment interruption study and elsewhere indicate that HIV infection may lead to an increased risk of myocardial infarction (MI), or heart attack. Two oral presentations at CROI dealt with this topic.

Matthew Freiberg from the University of Pittsburgh (abstract 809) presented an analysis of acute MI risk in the Veterans Aging Cohort Study. This study compared over 27,000 people with HIV to a matched group over 55,000 HIV negative veterans, followed from 2003 through 2008. The cohort is largely male and the average age was 49 years. Overall, the HIV negative veterans appeared to be at increased risk of MI due to some traditional risk factors, particularly diabetes and hypertension.

**Results**

- People with HIV had a 1.94-fold higher risk of having an acute MI during follow-up.
- The risk of MI from HIV was similar to that of diabetes and smoking in this study.
Among people who never smoked, HIV was still associated with increased MI risk. HIV positive and HIV negative people had MIs at the same average age, 53 years. After adjusting for other factors, class of antiretroviral drugs and CD4 cell count were not associated with MI risk.

These studies suggest that HIV infection increases a person's risk of cardiovascular disease including MI. But there is some evidence that effective treatment of HIV may reduce that risk. There is also evidence that advanced HIV disease contributes to a person’s risk of MI.

**Abacavir and MI Risk**

Abacavir (Ziagen, also in the Epzicom and Trizivir combination pills) is a widely used component of first line antiretroviral treatment. In 2008, an analysis of the D:A:D cohort found that abacavir was associated with an increased risk of MI.

Results from other studies, however, have proved conflicting. For example, GlaxoSmithKline, abacavir's manufacturer, performed an analysis of 54 studies in which abacavir was used and found no increased risk of MI. An analysis of the SMART study, in contrast, found a 4-fold increased risk of MI among those taking abacavir.

In a poster presentation at this year’s CROI, Xiao Ding of the U.S. Food and Drug Administration (abstract 808) presented a meta-analysis of 26 randomized controlled clinical trials (RCTs) in which abacavir was used. The analysis included almost 5000 participants, approximately 75% of the men. The researchers divided the studies into those sponsored by the manufacturer, the National Institutes of Health (NIH), and academic institutions.

**Results**

There was no statistically significant difference in MI rates between abacavir and non-abacavir trial arms.

The overall hazard ratio in the pooled studies was 1.02, not a significant difference.

Manufacturer and NIH studies both saw no increased risk; manufacturer's studies showed a hazard ratio of 0.70 while NIH studies showed 1.06.

Academic studies showed a hazard ratio of 1.6, but this was not considered statistically significant.

The results from this analysis are likely to fuel the ongoing controversy about abacavir and risk of MI. The controversy includes the classification of abacavir-containing regimens in the DHHS federal HIV treatment guidelines. The current guidelines classify regimens containing tenofovir/emtricitabine (Truvada) as "preferred" and those containing abacavir as "alternative." Abacavir was downgraded based in part on the D:A:D and SMART MI findings. 3/18/11

**References**


**Experts Warn Of Global Water Shortages Ahead Of World Water Day**

Speaking out ahead of World Water Day on Tuesday, water experts have warned of growing water shortages worldwide, Inter Press Service reports.

Currently, UNICEF estimates there are 884 million people worldwide who lack access to safe drinking water and 2.6 billion are without "adequate sanitation," the news service writes. U.N. Water predicts water shortages will only grow worse: "By 2025, 1.8 billion people will be living in countries or regions with absolute water scarcity, and two-thirds of the world population could be living under stress conditions," according to the group (Deen, 3/18).

"U.N. studies project that 30 nations will be 'water scarce' in 2025, up from 20 in 1990. Eighteen of them are in the Middle East and North Africa, with Libya and Egypt among those added to the 1990 list that includes Israel and Somalia," Reuters reports.
On Sunday, on the eve of a water and security meeting taking place this week in Canada, experts called on the U.N. Security Council to "promote 'hydro-diplomacy' to defuse any tensions over water in regions like the Middle East and North Africa where scarce supplies have the potential to spark future conflicts," the news service writes. "They said the U.N. Security Council should work out ways to bolster cooperation over water in shared lakes or rivers, from the Mekong to the Nile, that are likely to come under pressure from a rising world population and climate change" (Doyle, 3/20).

The three-day conference in Canada will bring together environment and policy experts to "discuss problems affecting the world's water supply," Canadian Press/CTV News reports. In addition to discussion about water and security issues, experts will look at "how water affects energy, development, the environment and public health," the news service writes (3/21).

The U.N. Environment Program on Monday issued a report (.pdf) on how rapid urbanization in Africa is creating new demands on water and sanitation services, Capital News reports (3/21). "Today 40 percent of Africa's one billion people live in urban areas – 60 percent in slums – where water supplies and sanitation are severely inadequate, according to the report," a UNEP press release states. "Africa's urban population without access to safe drinking water jumped from close to 30 million in 1990 to well over 55 million in 2008. ...Over the same period, the number of people without reasonable sanitation services doubled to around 175 million."

"Africa is the fastest urbanizing continent on the planet and the demand for water and sanitation is outstripping supply in cities," Joan Clos, executive director of UN-HABITAT, said, according to the press release. "As cities expand, we must improve our urban planning and management in order to provide universal access to water and basic services while ensuring our cities become more resilient to the increasing effects of climate change," Clos added (3/21).

**Scientists Refine Efforts To Develop Semi-Synthetic Artemisinin**

PostMedia News/Vancouver Sun reports on recent advances by researchers to speed the development of semi-synthetic artemisinin to treat people with malaria. Though artemisinin is currently derived "from the sweet wormwood plant found in parts of Asia and Africa ... cultivating and harvesting the plant and then extracting artemisinin is time-consuming and labour intensive," the news service writes. By introducing genes from the wormwood plant that give rise to artemisinin into yeast, researchers have shown they can boost the production of the compound. "The idea is to provide the developing world with antimalarial drugs at the lowest possible cost and, in addition, to provide a very stable supply because this yeast-fermentation process is shorter term and more reliable than growing the plants themselves," said Patrick Covello, a senior research officer at the National Research Council in Saskatoon, involved in the ongoing project. Covello said he "understands that Sanofi-aventis will begin commercial-scale production in 2012," according to the news service (Haight, 3/21).
Mutant Prions Help Cells Foil Harmful Protein Misfolding

ScienceDaily (Mar. 20, 2011) — Romping clumps of misfolded proteins are prime suspects in many neurological disorders including Alzheimer’s, Parkinson’s, and Creutzfeld-Jakob Disease. Those diseases are devastating and incurable, but a team of biologists at Brown University reports that cells can fix the problems themselves with only a little bit of help. The insight suggests that there are more opportunities to develop a therapy for protein misfolding than scientists had thought.

"There are multiple steps that you could target," said Susanne DiSalvo, a Brown biology graduate student and lead author of a paper published in advance online March 20 in Nature Structural and Molecular Biology.

In the study, the research team, led by Tricia Serio, associate professor of medical science, explains how two different beneficial mutant prions managed to foil the amplification of harmful clumps of misfolded proteins in yeast. Cells have an internal quality assurance system to break up and refold misfolded proteins, but that system can be overwhelmed by diseases. DiSalvo was the first to observe that the mutants act at distinct stages to tip the balance back in favor of the cells, allowing them to overcome the problem.

Serio says the molecular mechanisms appear to explain how similar mutants solve protein misfolding in mammals, including people. The phenomenon had been poorly understood and has never been exploited to develop a successful therapy.

Misfolding is a vulnerable process

Until now most scientists guessed that the only way to stop the runaway misfolding was right at the beginning and assumed the mutants must be blocking that first step to keep the protein in a harmless form. DiSalvo’s work instead suggests that there are many opportunities throughout the process where even a mild intervention could give cells what they need to gain the upper hand, Serio said.

"That's one of the biggest outcomes of Susanne's work: that if you just even slightly interfere with this process, the cell can deal with it and get rid of it," Serio said. "The dogma in the field is that these conformations were so abnormal the cell couldn't resolve them. But what we've found is that this process of misfolding is so efficient the cells can't keep up with it. If you make it even just a little bit less efficient the cell can get rid of the pathological state."

One mutant prion, Q24R, hinders the ability of misfolded proteins to aggregate into harmful clumps. It's like a dryer sheet that cuts down on static cling and makes it easier to fold laundry. Another helpful mutant prion known as G58D, assists the cell by speeding up its ability to unfold and refold misfolded proteins. That's more like a friend who helps untangle strings of holiday lights when they come out of storage.

DiSalvo’s experiments showed how the mutants and cells work together. Cells would only be cured when she both added a mutant and allowed the cells’ own quality assurance system to work. Adding the mutant G58D, for example, could cure a cell of infection by the Sup35 prion, but if she perturbed the cell’s quality assurance system then G58D would not work.

The results show the importance of delving deeply into molecular networks, said Stefan Maas, who oversees Serio’s and other cellular signaling grants at the National Institutes of Health.

"These results are a great example of the power of system-level studies," Maas said. "By showing how two beneficial mutants cure the cell of prions, this study has revealed that small changes applied to distinct components of a molecular network can dramatically alter the outcome for the cell. These new insights may lead to new strategies for preventing or treating disorders that involve protein deposits."

But those strategies may require turning proteins into pills. Serio noted that while beneficial mutant prions confer resistance to prion infection in nature, they haven’t been successful in reversing an established infection because sustained delivery into the body is too challenging. However, a small
molecule drug mimic, if developed, could target infected tissues more effectively over a longer period to slow or perhaps even reverse disease progression.

In the paper the researchers conclude, "A system-based approach to prion intervention represents a potentially promising direction in which to explore future therapies."

Other authors on the paper include Brown researchers Aaron Derdowski and John Pezza.

**Journal Reference:**

Susanne DiSalvo, Aaron Derdowski, John A Pezza, Tricia R Serio. Dominant prion mutants induce curing through pathways that promote chaperone-mediated disaggregation. Nature Structural & Molecular Biology, 2011; DOI: 10.1038/nsmb.2031

**Gut Bacteria Can Control Organ Functions**

ScienceDaily (Mar. 21, 2011) — Bacteria in the human gut may not just be helping digest food but also could be exerting some level of control over the metabolic functions of other organs, like the liver, according to research published this week in the online journal mBio®. These findings offer new understanding of the symbiotic relationship between humans and their gut microbes and how changes to the microbiota can impact overall health.

"The gut microbiota enhances the host’s metabolic capacity for processing nutrients and drugs and modulates the activities of multiple pathways in a variety of organ systems," says Sandrine Claus of the Imperial College of London, a researcher on the study.

Claus and her colleagues exposed germ-free mice to bedding that had previously been used by conventional mice with normal microbiota and followed their metabolic profiles for 20 days to observe changes as they became colonized with gut bacteria.

Over the first 5 days after exposure, the mice exhibited a rapid increase in weight (4%). Colonization also triggered a number of processes in the liver in which sugars (glucose) are converted to starch (glycogen) and fat (triglycerides) for short-term and long-term energy storage. Statistical modeling between liver metabolic functions and microbial populations determined that the levels of glucose, glycogen and triglycerides in the liver were strongly associated with a single family of bacteria called Coriobacteriaceae.

"Here we describe the first evidence of an in vivo association between a family of bacteria and hepatic lipid metabolism. These results provide new insights into the fundamental mechanisms that regulate host-gut microbiota interactions and are of wide interest to microbiological, nutrition, metabolic, systems biology and pharmaceutical research communities," says Claus.

Another important finding in the paper, according to Claus, is that gut colonization strongly stimulated the expression and activity of the cytochrome P450 3A11, an essential enzyme in drug-detoxification pathways.

Although she warns about being careful to extrapolate the specific findings from mice to humans, Claus notes the results of this research will provide a basis to further develop new strategies to beneficially modulate host metabolism by altering microbial communities in the gut.

**Journal Reference:**


**Poorly Presented Risk Statistics Could Misinform Health Decisions**

ScienceDaily (Mar. 21, 2011) — Choosing the appropriate way to present risk statistics is key to helping people make well-informed decisions. A new Cochrane Systematic Review found that health professionals and consumers may change their perceptions when the same risks and risk reductions are presented using alternative statistical formats.

Risk statistics can be used persuasively to present health interventions in different lights. The different ways of expressing risk can prove confusing and there has been much debate about how to improve the communication of health statistics.

For example, you could read that a drug cuts the risk of hip fracture over a three year period by 50%. At first sight, this would seem like an incredible breakthrough. In fact, what it might equally mean is that without taking the drug 1% of people have fractures, and with the drug only 0.5% do. Now the benefit seems to be much less. Another way of phrasing it would be that 200 people need to take the drug for three years to prevent one incidence of hip fracture. In this case, the drug could start to look a rather expensive option.
Statisticians have terms to describe each type of presentation. The statement of a 50% reduction is typically expressed as a Relative Risk Reduction (RRR). Saying that 0.5% fewer people will have broken hips is an Absolute Risk Reduction (ARR). Saying that 200 people need to be treated to prevent one occurrence is referred to as the Number Needed to Treat (NNT). Furthermore, these effects can be shown as a frequency, where the effect is expressed as 1 out of 200 people avoiding a hip fracture.

In the new study, Cochrane researchers reviewed data from 35 studies assessing understanding of risk statistics by health professionals and consumers. They found that participants in the studies understood frequencies better than probabilities. Relative risk reductions, as in "the drug cuts the risk by 50%," were less well understood. Participants perceived risk reductions to be inappropriately greater compared to the same benefits presented using absolute risk or NNT.

"People perceive risk reductions to be larger and are more persuaded to adopt a health intervention when its effect is presented in relative terms," said Elie Akl of the Department of Medicine, University at Buffalo, USA and first author on the review. "What we don't know yet is whether doctors or policymakers might actually make different decisions based on the way health benefits are presented."

Although the researchers say further studies are required to explore how different risk formats affect behaviour, they believe there are strong logical arguments for not reporting relative values alone. "Relative risk statistics do not allow a fair comparison of benefits and harms in the same way as absolute values do," said lead researcher Holger Schünemann of the Department of Clinical Epidemiology and Biostatistics at McMaster University in Ontario, Canada. "If relative risk is to be used, then the absolute change in risk should also be given, as relative risk alone is likely to misinform decisions."

**Journal Reference:**

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**High prevalence and incidence of anal pre-cancerous lesions in men with HIV; HAART has little impact**

Michael Carter
Published: 22 March 2011

Prevalence and incidence of high-grade pre-cancerous anal lesions in HIV-positive men who are taking antiretroviral therapy are high, Canadian investigators report in the online edition of *Clinical Infectious Diseases*.

A low nadir CD4 cell count and infection with HPV types 16 and 18 were associated with an increased risk of developing high-grade pre-cancerous anal lesions (AIN-2, 3).

The investigators hope that their findings will help identify patients who have a higher risk of HPV-associated anal disease.

Rates of HIV-related opportunistic infections have fallen significantly since the introduction of antiretroviral therapy.

However, the incidence of anal cancer is increasing.

Most of the information about the risk factors for this disease in HIV-positive gay men was obtained during the era before effective antiretroviral therapy became available. These include high-grade pre-cancerous lesions, infection with HPV 16 and 18, multiple HPV infections and CD4 cell count.

Investigators from the Canadian Human Immunodeficiency and Papilloma Virus Research Group (HIPVIRG) wanted to establish a comprehensive understanding of the risk factors for progression to AIN 2 and 3. They also wished to see if treatment with anti-HIV drugs had any impact on disease progression.

A total of 247 men who were taking or about to initiate antiretroviral therapy were recruited to the study between 2002 and 2005.

The patients had swabs to see if they had anal HPV infection, and if present further tests were conducted to determine whether strains associated with anal cancer were present.

At baseline and then at intervals of six or twelve months the patients underwent high-resolution anoscopy to check for pre-cancerous lesions.

Median age at baseline was 43 years, 38% were smokers (a risk factor for HPV-related cancers), 90% were already receiving HIV therapy, median CD4 cell count was 380 cells/mm³ and 54% had an undetectable viral load.

On entry to the study, 19% of patient had normal anal cytology, 50% had low grade lesions, AIN 2 was present in 17%, and 13% had AIN 3.
Follow-up was for a median of 38 months. High-grade anal lesions were identified at least once in 54% of patients. However, only two patients developed anal cancer.

A total of 147 who did not have AIN 2 or 3 at follow-up were followed so that the investigators could calculate rates of progression and risk factors.

Incident high-grade lesions were diagnosed in 57 patients, and this provided a rate of 12.8 cases per 1000 months of follow-up. The cumulative incidence was 23% after two years and 37% after 36 months.

Analysis that included men whose first two anoscopy results negative for high grade lesions showed a progression rate of 7 cases per 1000 person months and an 24-month incidence of 21%.

Risk factors for the development of AIN 2 or 3 included older age (40-49 years, OR = 3.09; 95% CI, 1.12-8.52; over 50, OR = 4.78; 95% CI, 1.29-17.73); a nadir CD4 cell count below 50 cells/mm³ (OR = 14.40; 95% CI, 1.45-143.58); infection with HPV 16 or 18 (OR = 14.18; 95% CI, 3.51-57.32), and infection with HPV 16 and 18 (OR = 3.10; 95% CI, 5.68-169.60).

Current CD4 cell count was not associated with disease progression, and there was only very modest evidence that therapy with anti-HIV drugs had a protective effect. Incidence of AIN 2 and 3 was slightly reduced among patients who had been taking HIV treatment for four or more years.

“We...found that men who had received their current HAART regimen for a longer time had a lower risk...especially after adjusting for nadir CD4 cell counts. This suggests that, although one cannot fully recover from HIV-induced immune deficiency, HAART could have some beneficial effect in reducing the risk of AIN-2,3,” comment the authors.

They conclude, “our study confirms the high prevalence and incidence of AIN-2,3 among HIV-infected MSM.”

Patients with a low nadir CD4 cell count could, the investigators believe, especially benefit from screening for pre-cancerous lesions. In addition, “typing could also be useful as an adjunct to cytological examination in primary screening.”

The author of the accompanying editorial believes the study “may being us closer to the identification of biological markers of AIN progression and provide a practical screen tool for anal HPV disease.

Reference
1. de Pokomandy A et al. HAART and progression to high-grade anal intraepithelial neoplasia in men who have sex with men and are infected with HIV. Clin Infect Dis, online edition, doi: 10.1093/cid/cir064, 2011 (click here for the free abstract).

Monday, March 21, 2011

Justice Department Issues Letter Regarding Illegal Exclusion of Individuals with HIV/AIDS from Occupational Training and State Licensing

WASHINGTON – The Justice Department has issued letters to the attorneys general of all 50 states, as well as U.S. territories to request their assistance in addressing the illegal exclusion of individuals with HIV/AIDS from occupational training and state licensing. Persons with HIV and persons with AIDS are covered by the Americans with Disabilities Act (ADA), which gives federal civil rights protections to persons with disabilities in public accommodations, employment, and state and local government services.

The Justice Department has learned that public and private trade schools for barbering, cosmetology, massage therapy, home health care work and other occupations, as well as state licensing agencies, may be illegally denying individuals with HIV/AIDS admission to trade schools and/or occupational licenses because of their HIV status. However, because HIV cannot be transmitted by casual contact or by the circumstances present in these occupations, HIV-positive status is irrelevant.

In his letter to the attorneys general, Assistant Attorney General for the Civil Rights Division Thomas E. Perez asked that they review their respective jurisdictions’ admission and licensing criteria for trade schools and licensing agencies to identify the existence of any criteria that unlawfully exclude or discriminate against persons with HIV/AIDS, and to take the steps necessary to bring all such programs into compliance with the ADA.

“It is critical that we continue to work to eradicate discriminatory and stigmatizing treatment towards individuals with HIV based on unfounded fears and stereotypes,” Assistant Attorney General Perez said. “The ADA clearly protects individuals with HIV and other disabilities from this kind of exclusion or marginalization.”

The department recently entered into a settlement agreement with Modern Hairstyling Institute Inc., a private cosmetology school in Bayamón, Puerto Rico, for delaying the admission of an HIV-positive
individual. That settlement agreement requires the school to remove questions about applicants’ HIV/AIDS status and to promptly enroll the aggrieved individual in its cosmetology program. The department has also addressed related issues in its guidance entitled “Questions and Answers: The Americans with Disabilities Act and the Rights of Persons with HIV/AIDS to Obtain Occupational Training and State Licensing” (www.ada.gov/qahivaidsl_license.htm).

Sex Education Bill Signed

Clarion Ledger (Jackson), (03.17.2011) Marquita Brown
Gov. Haley Barbour has signed into law HB 999, a measure that requires Mississippi public schools to provide sex education.

Previously, the state did not require school districts to teach sex education but those that did had to use an abstinence-only curriculum. Under the new law, districts must begin teaching sex education by the end of June 2012. The state standard will continue to be abstinence-only, though districts can elect to adopt an “abstinence-plus” approach, which covers topics such as contraception.

Districts “must choose one or the other,” said Rep. John Mayo (D-Clarksdale). “You’re not just going to ignore this problem.”

In 2009, the latest year for which data are available, Mississippi led the nation in teenage births. Also that year, CDC’s Youth Risk Behavior Survey indicated 61 percent of high school students in the state had engaged in sexual activity—the national average was 46 percent.

HB 999 gives local school boards “the authority to select the policy that they think is right for their community,” said state Department of Education spokesperson Wendy Polk. “We will work with each district to provide training and resources to help them with their curriculum.” Districts will be required to report which choice they make, allowing the department to study what works.

The law stipulates that students be divided by gender for sex education instruction, forbids condom use demonstrations, and maintains that abortion cannot be included as a means of birth control. Parents will be able to opt their child out of the classes.

Mayo noted that some dissenters have asked what business the state has in teaching children about sex. “The state has a financial responsibility because the health care costs for teenage pregnancies for unwed mothers are enormous,” he said.

Drug Resistance Hampers Fight Against Tuberculosis

Reuters, (03.18.2011) Kate Kelland
The growth in the rate of multidrug-resistant TB is threatening progress in the global TB fight, experts said Friday.

The spread of MDR TB continues to be a concern in Europe, according to a new report by the World Health Organization and the European Center for Disease Prevention and Control. Reported TB rates overall have been declining in Europe since 2005, standing at a regional average of 36.8 notifications per 100,000 population in 2009, according to WHO-ECDC. However, newly diagnosed and relapsed TB cases in 18 high-priority countries in the region are nearly eight times higher than the rest of Europe. Most of the high-priority nations are neither members of the European Union nor part of the European Economic Area, WHO-ECDC said.

“Vulnerable populations, including children, still do not have ready access to quality and timely diagnosis and treatment,” said WHO-ECDC. “This remains a matter of urgency given the high prevalence of multi- and extensively drug-resistant TB in the region.”

“Increasing rates of drug-resistant TB in Eastern Europe, Asia, and sub-Saharan Africa now threaten to undermine the gains made by worldwide TB control programs,” researchers said in a separate new report in the Lancet. TB kills 1.7 million people globally each year, and the more than 9 million new cases annually is a historical high, said Alimuddin Zumla of the University College London Medical School and Stephen Lawn of the University of Cape Town.

Experts cite HIV/AIDS, rising global rates of diabetes, and high rates of smoking in low- and middle-income countries as key drivers of TB. Diabetes raises the risk of TB three-fold, and smoking increases it two-fold, the Lancet authors reported. Global TB control is being hindered by the lack of cheap and quick diagnostics, long treatment regimens, absence of an effective vaccine, rising MDR TB rates, and weak health systems, they said.

Social Messages, Social Context, and Sexual Health: Voices of Urban African-American Youth

*American Journal of Health Behavior Vol. 35: No. 2: P. 162-174* (03.04.2011) Molly Secor-Turner, PhD, RN; Renee Sieving, PhD, RN; Ann Garwick, PhD, FAAN, RN

The study authors aimed to “describe aspects of the social context that low-income, urban African-American young women articulate as having influenced social messages they received during adolescence about pregnancy timing and childbearing.”

Individual interviews were conducted with 20 African-American females ages 18-22.

Five themes emerged from the results: “first sex; getting ready and getting it over with; the path for African-American girls; gender expectations: insecurity and independence; living into a future; and living in a context of instability and uncertainty.”

The study’s findings highlight the “complex relationship between social context, social messages, and decisions about pregnancy timing and childbearing,” the authors concluded.

Speakers at Forum Debate Condoms in City Schools

*Rochester Democrat and Chronicle*, (03.17.2011) Patti Singer

At a health forum on March 16, Rochester’s school board solicited community feedback in response to a January presentation about sexual activity and HIV cases among area young people.

Of 78 HIV diagnoses reported in Monroe County last year, 35 were in people younger than 25, the board heard during the January presentation. Of teens reporting sexual intercourse, 61 percent used a condom during the last encounter, said Dr. Andrew Doniger, the county health director.

“Another way of looking at that is 39 percent didn’t,” Doniger said. “That’s risky for that 39 percent.”

“I know we have a serious issue in our community with [STDs], HIV and AIDS,” said Cynthia Elliott, chair of the Community and Intergovernmental Relations Committee, which hosted the forum.

“Something has to be done. Is it the school district necessarily? I don’t know.”

“We really want to hear what the community is saying,” said Jose Cruz, chair of the Policy Development and Review Committee. “Will we please everyone? No. But we’ll address their concerns and make the best decision possible.”

Qualified outside agencies should be allowed to teach about sexuality, and sexually active students should have access to condoms, said Sheila Driscoll, director of Metro Council for Teen Potential.

Parents struggle with how to discuss sex, and the spiritual and emotional aspects of it are often neglected, said the Rev. George Nicholas, pastor of Grace United Methodist Church. “Instead of saying ‘Just don’t do it,’ we need to be open to having a conversation,” he said.

Many teens said their peers would continue to have sex in any case, and that making condoms available at schools would give them a trusted place to go. But retired doctor Barbara Fredericks said condoms deny the necessity of self-control, while others said condoms give teens a false sense of safety.

Evolution Project for Black Gay Men Opens New Facility

*Georgia Voice (Atlanta)*, (03.18.2011) Ryan Lee

Atlanta’s Evolution Project, which helps young black men who have sex with men (MSM) navigate the transition to adulthood, recently moved to the heart of the city’s heavily gay Midtown neighborhood, nearly tripling its space in the process.

Funded by CDC grants, Project Evolution was created in 2006 by AID Atlanta to promote HIV prevention among young black MSM, a population particularly at risk. Though prevention remains key to its mission, the project has broadened its scope considerably. “We want to make sure our programming reflects the diversity of the community,” said Kevin Hatcher, activities and linkages coordinator.

Regular programs include support groups for both HIV-negative and HIV-positive males; a workshop on dating; a physical education program discussing topics from yoga to anal health; a writers’ group; a book club; a facilitated weekly session in which members open up about the stresses and realities of young black life; and a group especially for young professionals and graduate students.

“It’s like being in an environment that’s more accepting to the way I am,” said one young man. “It can teach you a lot of things about protecting yourself from STDs and things like that, and it’s a good place to come if you’re just coming out of the closet ... because it shows you that it’s OK to be who you are, and gives you the support of your peers.”
“We’re all about empowerment here, so it’s not just a place you come when you need something, it’s also a place for you to come when you want to grow, when you want to hang out, when you want to be involved in something,” said Hatcher.

For more information on Project Evolution, visit www.evolutionprojectatl.org.

**Queen’s University puts over 2,400 food scares under the microscope**

As the increasing number food scares causes consumers to question the safety of everyday food items, researchers at Queen’s University Belfast have completed the first ever analysis of all the food recalls announced in the USA, UK and Ireland over the last decade.

The research, by Dr Antony Potter at Queen’s Centre for Assured and Traceable Foods (ASSET) identified 2,439 food recalls over the past ten years – including the recall of 380 million eggs in the USA in 2010 following a Salmonella outbreak at a farm in Iowa, and the 2008 pork recall in Ireland, which affect export markets in 21 countries around the world.

The research will be discussed during *The Food Integrity and Traceability Conference* taking place at the University this week (21-24 March). This international event, held in partnership with *safefood*, will showcase the latest developments in food safety and traceability.

Dr Potter said: “The number of food scares and product recalls has increased significantly in the past decade. Until now, however, there has been no international database to measure trends in food recalls.

“Our detailed analysis of recalls in the UK, Ireland and USA begins to help fill that gap. It outlines how the frequency and severity of recalls has increased over the past ten years, accompanied by significant financial implications for food producers. The 2008 pork recall in Ireland, for example, cost the Irish economy an estimated €125 million.

“Of the product recalls we identified, 68 per cent were detected during routine or spot testing by regulatory bodies, and only 21 per cent were detected by the company in question. Around one fifth (21 per cent) were in the meat industry, 12 per cent in processed foods and 11 per cent in fruit and vegetables.

“Most recalls (56 per cent) resulted from operational mistakes, such as incorrect labelling, the presence of an undeclared ingredient, or contamination during the production. While biological causes, such as the detection of Listeria, Salmonella and E Coli were also a factor, a significant number of food safety alerts were actually due to food fraud and corruption by suppliers further down the supply chain. This highlights the need for food producers to invest in ensuring the traceability of their products back through the supply chain.”

Dr Potter is one of 40 speakers from more than 20 countries who will address *The Food Integrity and Traceability Conference* this week. Professor Chris Elliott from Queen’s School of Biological Sciences has organised the conference.

Professor Elliott said: “Despite mounting evidence of the increasing levels of food fraud, and growing public demand for safe and authentic food, this is a topic that few in the food industry appear willing to talk about openly for fear of the repercussions for their brand.

“Food producers, however, should be reassured that major scientific advancements are being made to help detect food contaminants and minimise risks to the food supply chain. Scientists at Queen’s are at the forefront of these developments, and we are willing to work with companies to put in place the latest techniques to detect and deter food fraud. And many of these techniques will be discussed during this week’s conference.”

The conference is jointly organised by Queen’s and *safefood*, the North-South body responsible for the promotion of food safety on the island of Ireland. Dr Gary Kearney, Director, Food Science, *safefood* said: “The increase in the number of food scares since the early 1990’s has had a negative impact on consumer confidence in the food supply chain. To restore confidence and allay consumer concerns, it is vital that new scientific methods are developed which can detect harmful toxins early in the production of food, thereby facilitating appropriate containment measures and ensuring consumer protection.

“This conference will highlight the latest scientific methodologies for controlling food safety hazards as well as the challenges to providing robust food traceability systems. These and other issues are essential to the provision of safe food and protecting consumers on the island of Ireland.”

Among the conference highlights will be Professor Garry Lee from the University of Western Australia and TSW Analytical P/L, who will present a new traceability system being trialled in the Australian pork industry and its lessons for the UK and Ireland pork industry following the Irish pork contamination scare of 2008.
As the demand for organic food continues to grow, Dr Simon Kelly from Defra's Food and Environment Research Agency will present some of the latest techniques in determining the origins of food and whether or not those labelled 'organic' are truly organically produced.

Owen Brennan, Managing Director of Belfast-based agri-technology company Devenish Nutrition, will discuss the controversial EU ban on GM crops and its negative impact on ensuring a sustainable EU food production system; while Professor Peter Shears from the University of Plymouth Law School will speak about the lack of resources being invested in the fight against food fraud.

Newly discovered virus implicated in deadly Chinese outbreaks
Tick-borne disease identified as emerging threat

GALVESTON, Texas — Five years ago, large numbers of farmers in central China began falling victim to an mysterious disease marked by high fever, gastrointestinal disorder and an appalling mortality rate — as high as 30 percent in initial reports. Investigators from the Chinese Center for Disease Control and Prevention hurried to the scene of the outbreak. On the basis of DNA evidence, they quickly concluded that it had been caused by human granulocytic anaplasmosis, a bacteria transmitted by tick bites.

Now, though, subsequent studies have shown that original conclusion was incorrect, and that a previously unknown and dangerous virus has been responsible for seasonal outbreaks of the disease in six of China's most populated provinces.

"We expected to find a bacterial infection behaving in an unexpected way — human anaplasmosis has a less than one percent fatality rate in the U.S., and it rarely causes abdominal pain or vomiting or diarrhea," said Dr. Xue-Jie Yu of the University of Texas Medical Branch at Galveston, lead author of a paper on the discovery now appearing in the "online advance" section of the New England Journal of Medicine. "Instead, we found an unknown virus."

Researchers have dubbed the newly discovered pathogen Severe Fever with Thrombocytopenia Syndrome virus, and placed it in the Bunyaviridae family, along with the hantaviruses and Rift Valley Fever virus. Later investigation has placed its mortality rate at 12 percent, still alarmingly high.

Yu, a specialist in tick-borne bacteria like the species responsible for HGA, first suspected that a virus might be responsible for the outbreaks after close examination of patients' clinical data showed big differences from symptoms produced by HGA, and blood sera drawn from patients revealed no HGA or HGA antibodies.

Yu became certain that a virus was at fault after sera taken from patients retained its ability to kill cells, despite being passed through a filter that blocked all bacteria. Still, initial genetic tests failed to generate a match with a known pathogen.

"Clearly, we had a virus, but what virus?" Yu said. "I told the people I was working with that they needed to be even more careful, because we were working with an unknown."

That caution seemed appropriate when electron microscope studies of deactivated virus particles revealed what appeared to be a hantavirus — associated in Asia with hemorrhagic fever and in the Americas with a deadly pulmonary syndrome. But when Yu and his colleagues managed to extract the virus' entire genetic code, they found that it didn't match any other known virus.

When researchers from the Chinese Center for Disease Control and Prevention led by study author Dr. Yu Wang analyzed sera taken from 241 symptomatic patients from Henan, Hubei, Shandong, Anhui, Jiangsu and Liaoning provinces, they found 171 contained either the previously unknown virus itself or antibodies against it. In addition, the scientists found the virus in 10 out of 186 ticks collected from farm animals in the area where the patients lived.

"This seems to be a tick-borne disease, and the disease comes out when the ticks come out, from late March to late July," Yu said. "Fortunately, even though the full life cycle is not clear, we know that for the virus humans are a dead end — we don’t have human-to-human transmission as we did with SARS."

How Different Strains of Parasite Infection Affect Behavior Differently

ScienceDaily (Mar. 21, 2011) — Toxoplasma gondii infects approximately 25 percent of the human population. The protozoan parasite is noted for altering the behavior of infected hosts. Jianchun Xiao and colleagues of the Johns Hopkins School of Medicine find clear differences in the manipulation of host gene expression among the three clonal lineages that predominate in Europe and North America, "despite the high level of genetic similarity among them," says Xiao. Type I infection largely affects genes related to
the central nervous system, while type III mostly alters genes that modulate nucleotide metabolism. Type II infection does not alter expression of a clearly defined set of genes.

The research is published in the March 2011 issue of the journal *Infection and Immunity*.

Indeed, *T. gondii* can play its infected rodent hosts like a piano, converting rats’ and mice’s natural aversion to feline odors into an attraction, presumably to enable the parasite’s sexual cycle. *T. gondii* can reproduce sexually only in cats. Investigations of effects on humans have found an increased risk of traffic accidents, and other reckless behavior, as well as links to hallucinations.

"*Toxoplasma* infections, at least for mice, are so variable in their severity and heavily dependent on which strain is doing the infecting," says Xiao. "Understanding the differential effects caused by these strains could enable predicting the outcome of infection and point out directions to be explored in future studies to eliminate transmissions or cure disease. If *Toxoplasma* is linked to schizophrenia, this could lead to new treatments of that disease as well."

"It is noteworthy that we found vasoactive intestinal peptide receptor 2 (VIPR2) was upregulated by all three *Toxoplasma* strains," says Xiao. VIPR2 "is linked to schizophrenia in some recent publications. Since the tropism of *Toxoplasma* for brain has been linked with specific behavioral changes and psychosis in humans, this finding will have some fundamental significance for understanding the correlation between *Toxoplasma* and psychosis."

Type II strains cause 70–80 percent of human cases reported in North America and Europe.

**Journal Reference:**

**Fewer Bats Carry Rabies Than Thought**

ScienceDaily (Jan. 31, 2011) — Bats tend to have a bad reputation. They sleep all day, party at night, and are commonly thought to be riddled with rabies. A study by University of Calgary researchers has confirmed that bats are not as disease-ridden as the stigma suggests.

"The notion that bats have high rates of rabies is not true," says Brandon Klug, a graduate student at the University of Calgary and the lead author of a paper published in the *Journal of Wildlife Diseases*.

"Those of us that work with bats have always known the rates are low; and now we have evidence that bats aren’t disease-ridden vermin their reputation would have you believe."

Previous studies have suggested that typically about 10 per cent of bats taken by the public to be tested have the disease and prevalence varies greatly, depending on the species and how often that species is around people. But University of Calgary research says the number is closer to one per cent regardless of species or where the bats roost.

Researchers compared bats turned in by the general public and those randomly sampled from their natural environment. In the field, they looked for the disease in carcasses of migratory tree-roosting hoary bats (*Lasiurus cinereus*) and silver-haired bats (*Lasionycteris noctivagans*) killed by wind turbines. These species are among bat species with the highest reported prevalence of rabies in North America. At the same time they compared these bats with rabies prevalence from literature contained in public health records in North America.

"This study is significant because it confirms that rabies rates for bats has been over-estimated. It’s also the first time such a rigorous literature review has been completed on this topic," says co-author Dr. Robert Barclay, biological science professor and head of the Department of Biological Sciences at the University of Calgary.

University of Calgary researchers sent 217 carcasses to the Centers of Disease Control and Prevention in the U.S for testing. They also reviewed the literature on reported rabies in multiple bat species in North America covering the past 56 years, which included 65,096 bats.

Bats, along with other species including foxes, skunks and raccoons, are considered reservoirs for the disease. Rabies is passed from bat to bat at a rate that keeps the virus in the population, but rarely fast enough to eradicate the bat population or slow enough to result in the demise of the virus.

"Since the background rabies rate in bats is low, less than one percent, people should focus more on the ecosystem services they provide without worrying that every other bat has rabies. This is especially important right now because bats are facing some heavy threats, like wind turbines and white nose syndrome," says Klug.

"With that said, healthy bats normally don’t come in contact with people, so those that do are more likely to be sick, so we’re not encouraging people to go out and handle them."
A Better Test for Human Papillomavirus

ScienceDaily (Mar. 21, 2011) — A new test for human papillomavirus (HPV) is just as sensitive as the old one, but more specific for detecting cervical cancer, meaning that it has fewer false positive results, according to a paper in the February 2011 Journal of Clinical Microbiology.

"This is important because reducing false positive results avoids unnecessary additional tests and follow-up, the associated health care costs, and distress to women," says first author Sam Ratnam, of the Faculty of Medicine, Memorial University, St. John’s, Newfoundland and Labrador. HPV infection, he explains, is highly prevalent, but "only a small fraction of the infected are at risk of developing HPV-associated cancers."

The investigators report that the new test, called the Aptima HPV test, detected 96.3 percent of women with high-grade cervical intraepithelial neoplasia or worse (CIN 2+) compared to 94.3 percent for the old test, the Hybrid Capture 2 DNA test (HC2), among 1418 women studied. But Aptima has far fewer false positives than HC2. "This difference could be attributed to the fact that the Aptima test detects the expression of two oncogenes, E6 and E7, via their messenger RNAs," says Ratnam. "These proteins are involved in initiation and mediation of oncogenic process that leads to cervical cancer, and to other HPV-associated cancers. The HC2 test, on the other hand, detects the viral DNA which is not as discriminating. The Pap smear, the traditional common screening method for cervical cancer, has few false positives, but fails to detect nearly half of all CIN 2+ cases."

While HPV is the single most common sexually transmitted virus, its spread is increasing due to rising oral sex among young people, according the Oral Cancer Foundation. "We're seeing more and more cases of tonsilar cancers in Newfoundland," a cancer which is frequently caused by HPV, says coauthor Adrian Lear of the Dr. H. Bliss Murphy Cancer Centre, St. John’s, Newfoundland. In people under the age of 50, HPV-associated oral cancers may even be replacing tobacco as the primary causative agent according to the Oral Cancer Foundation.

While the role of HPV is most recognized in cervical cancer, it is also associated with anal and penile cancers, and cancers of the vagina and vulva. The test could detect HPV infections that have begun to progress towards these other HPV-associated cancers, says Ratnam.

Currently, two vaccines are available against HPV: Gardasil, which is active against four types, 16, 18, 6 and 11, and Cervixx, which is active against two types, 16 and 18. Types 16 and 18 account for about 70% cervical cancer world-wide, and types 6 and 11 account for over 90% of genital warts. These vaccines are now approved in many countries around the world but offered only to females. "I'm convinced the day is coming when the vaccine will be offered for both males and females through publicly funded programs," says Lear. "In the meantime, the use of a more accurate test such as the Aptima test should improve the efficiency and cost-effectiveness of cervical cancer screening around the world, and should help prevent cervical cancer," says Ratnam.

AIDS Tests Come to South Africa's Schools

Agence Franche Presse , (03.16.2011)

At a high school in Mtubatuba, some students recently underwent HIV testing at a mobile clinic brought in by Mpilonhle (Zulu for “good health”). Since 2007, the charity has sent teachers, social workers, and nurses to local schools. However, it is one of just a handful of organizations that offer school-based HIV testing in South Africa.

By age 16, half of South African youths have experienced sex, and 9 percent have acquired HIV by age 20. In February, the government endorsed expanded HIV testing for all students older than 12, even though some advocates worry that children will feel coerced and be emotionally unprepared for an HIV-positive diagnosis.

“We underestimate adolescents’ knowledge,” said pediatrician Michael Bennish, who founded Mpilonhle. “All adolescents, by definition, have elements of maturity and immaturity. With proper support and good counseling which is friendly to them, they can make a mature decision.”
“I feel happy, I am able to tell my mum,” said Nkosi Minenhle, 15. “And I know how to behave to remain negative.”

About one-quarter of students declined Mpilonhle’s rapid-testing offer.

“I am afraid,” said one 17-year-old at Madwaleni high school, who has had sex with an older man and fears she has HIV. “Once I know that I am positive, my school work will be affected.”

“You can’t pretend that these teenagers are not sexually active, when they are,” said Gugu Zulu, Mpilonhle’s top educator. “They are no longer innocent angels.”

“Because most parents are unemployed, to get things the kids will go out with sugar daddies to get money from them,” said Andile Zulu, a Mpilonhle social worker. Of 12th-graders tested, 6 percent of females were HIV-positive, compared with less than 3 percent of boys.

Could a Transmissible Treatment Help Curb HIV Epidemic?

As reported in a recent issue of the open-access journal *PLoS Computational Biology*, researchers studied therapeutic interfering particles (TIPs), virus-like particles that can disrupt the functioning of HIV.

If TIPs could “piggyback” on HIV in individuals who engage in risky behavior, they might have a significant effect on the epidemic by lowering transmission in the most high-risk and hard-to-reach populations.

Below is a press release issued by the University of California at San Diego describing the study.

**Transmissible Treatment Proposed for HIV Could Target Superspreaders to Curb Epidemic**

March 17, 2011—Engineered, virus-like particles would hitch a ride with HIV to reach high-risk populations that don't seek or comply with medical treatment and are responsible for a disproportionate share of the spread of disease, a new model demonstrates.

Biochemist Leo Weinberger and colleagues at the University of California, San Diego and UCLA have proposed a fundamentally new intervention for the HIV/AIDS epidemic based on engineered, virus-like particles that could subdue HIV infection within individual patients and spread to high-risk populations that are difficult for public health workers to reach.

With a model that considers the effects of the proposed treatment on several scales, from interference with HIV in infected cells to viral loads in individual patients to the prevalence of HIV in large populations, they determined that the engineered particles could work in concert with current treatments for HIV infection and lower the prevalence of infection more effectively than current drugs or proposed vaccines alone. Their findings will appear in the March 17 issue of *PLoS Computational Biology*.

"Dr. Weinberger's idea to use engineered virus-derived particles to combat infectious diseases is truly provocative," said James Anderson, M.D., Ph.D., Director of the Division of Program Coordination, Planning, and Strategic Initiatives. Anderson oversees the NIH Common Fund, which supports a series of exceptionally high impact, trans-NIH programs including the NIH Director's New Innovator Award, which Weinberger received in 2009.

The engineered particles, called therapeutic interfering particles or TIPs, would persist for years in an individual patient and could be packed with genes that disrupt the functioning of HIV. Weinberger's team has succeeded in creating functional prototypes in the lab.

"TIPs are molecular parasites that 'piggyback' on HIV to spread between individuals," Weinberger said. The engineered particles use the same outer envelope as HIV but lack the genes for components of this structure and the enzymes needed to assemble it. They can only replicate, infect additional cells and transmit to new individuals by stealing these elements from HIV. Until the host cell is infected with HIV, TIPs remain dormant.

In an HIV-infected individual, TIPs would transmit to others in the same ways as the natural virus—through unprotected sex or shared needles, for example. That means TIPs would, by design, penetrate high-risk populations that are responsible for a disproportionate share of the spread of disease and can be particularly difficult for public-health officials to reach.

Using an epidemiological model, Weinberger and colleagues compared the predicted effects of the treatment they propose with current drug campaigns and hypothetical vaccines and found that TIPs could be more effective.
An intervention using TIPs could lower the number of people infected with HIV in sub-Saharan Africa
to one thirtieth the current level in about 30 years, they found. Optimistic predictions for vaccine
campaigns or currently available antiretroviral therapy would lower the number of HIV-infected people
by less than one half the current level over the same period of time.

TIPs wouldn't replace other therapies, Weinberger said, "In part, we are arguing that TIPs could be
used in conjunction with current antiretroviral drug therapy or vaccine campaigns, and could enhance the
efficacy of these campaigns at the population level."

Weinberger acknowledges that an infectious treatment raises ethical concerns and is working with
bioethicists to explore the unique issues associated with any use of TIPs in more detail.

He also points out that vaccines already in use can spread from one person to another. People who
receive the oral polio vaccine, for example, "shed" the weakened version of the virus that is the basis of the
vaccine and this can transmit immunity to other individuals. Public health officials see this transmission
as a benefit; it is one reason why this form of polio vaccine was chosen for the worldwide effort to
eradicate the disease.

Reference

**Chikungunya: The Key Role of 'Innate Immunity'**

ScienceDaily (Mar. 23, 2011) — Chikungunya is transmitted by mosquitoes of the genus Aedes. The
disease is spreading in the world and periodically sparks new outbreaks. Africa, Asia, the Indian Ocean
and even Southern Europe are now affected. The viral infection can be expressed in many different ways.
Patients can suffer forms ranging from a simple fever to severe pain in the joints. This high variability in
symptoms arises from the variability of humans' individual immune defence systems.

Blood analyses conducted during the 2007 Gabonese epidemic, studied by IRD researchers and their
partners, recently showed the key role of innate immunity, the organism's first line of defence, in the
clinical course of the infection. Control of the disease thus closely depends on the underlying
configuration of each patient's immune system. The serious cases would therefore be due to a defect in the
innate response, as happens in pregnant women, the aged, and other vulnerable groups. These
investigations have brought new insights into this disease, insufficiently studied and neglected by public
authorities.

Chikungunya virus, first isolated in Tanzania in 1953, caused a great number of epidemics in Africa
and South-East Asia in the course of the 20th Century.

**A global threat**

This infectious disease, like yellow fever and dengue, is caused by an arbovirus, transmitted by blood-
sucking arthropods, ticks and Phlebotominae or sand flies. Its main vectors are mosquitoes of the genus
Aedes. Particularly concerned is *Aedes albopictus*, nicknamed the "tiger mosquito," whose eggs enable it
rapidly to conquer new territories. Increasing human travel, which spreads the larvae, and the rising
resistance of mosquitoes to insecticides have contributed to the rapid expansion of epidemics over the
past few years, to new regions of the world: islands in the Indian Ocean, Central Africa and even, very
recently, Southern Europe are now affected. The outbreak in Réunion Island in 2005-2006 hit over 260
000 people. The recent epidemic in southern Italy, in 2007, and also the first reported case of fever in the
South of France illustrate the potential for world-wide diffusion, making this disease, rarely fatal but
severely incapacitating, a major threat to public health.

**Strong innate immunity**

Ranging from a simple bout of fever to severe pain in the joints, chikungunya can take on many different
forms. This very broad variability of symptoms is due to variations in the individual immune response of
each patient. IRD researchers and their partners1 recently showed the key function of "innate immunity,"
the organism's first line of defence, in the clinical course of the disease.

Challenged by the presence of foreign DNA in the organism following a viral, bacterial or parasitic
infection, or the presence of tumoral cells, the organism activates its immune system. This immune, or
inflammatory response, occurs in two major stages: non-specific defence, also called "innate immunity,"
which does not take account of the nature of the micro-organism it is fighting, and the specific response,
which targets the pathogenic agent in the infected cells.

In chikungunya patients, the first stage response is highly effective. Detailed analysis of nearly 70
blood plasma profiles taken during the 2007 epidemic in the Gabonese capital Libreville, revealed the
presence, during the first four days of symptoms, of a high quantity of interferons, cytokines and
chemokines,* immune-system substances akin to hormones- Interferons play a prime role in the immediate inflammation defence system. As the name indicates they interfere with replication of the virus in host cells and thus inhibit the virus early in the process. The function of cytokines and chemokines is to activate the second stage: the specific response. These proteins attract immune cells -leucocytes- to each virus replication site and direct the deployment of the organism's antiviral defences.

Control of the disease therefore depends closely on the underlying immune status of each patient. Severe cases could therefore be the result of a defect in the innate response mechanism, as can occur in pregnant women, elderly people or Aids patients.

A highly disabling disease
Serious forms can consequently appear, inducing highly disabling stiffening of the joints, the reason for the name of the disease: chikungunya meaning "bent man disease" in the Makonde language of Southern Africa. These symptoms generally last three to seven days, the time for the immune cells to work, but can also become chronic and persist for months, even years. Neurological and hepatic complications can also occur in the most severe forms. There is currently no specific treatment, so therapeutic care aims solely to alleviate these symptoms, using analgesic and anti-inflammatory drugs.

Medical professionals are at the dawn of their research on the disease, long neglected by government authorities. The research team is similarly exploring the role, in pathogen inhibition, of cells called Natural Killer, capable of killing directly the infected cells. In parallel, investigations are also under way on modulation of the immune response in cases of co-infection with dengue virus, recently discovered in Gabon, a new threat involving a simultaneous attack by the two severely debilitating diseases.

* Interferons, cytokines and chemokines are proteins produced by the cells of the immune system.

Journal Reference:

The Killer Within: A Novel Bacterial Suicide Mechanism
ScienceDaily (Mar. 22, 2011) — The zeta toxins are a family of proteins that are normally present within various pathogenic bacteria and can mysteriously trigger suicide when the cells undergo stress. A team led by Anton Meinhart at the Max Planck Institute for Medical Research in Heidelberg has now found the mechanism underlying this programmed bacterial cell death.

Their paper, publishing in the online, open access journal PLoS Biology, reports that zeta toxins convert a compound required for bacterial cell wall synthesis into a poison that kills bacteria from within. In the future it may be possible to hijack this mechanism for bacterial defense and to design drugs that mimic these toxins.

Most bacteria harbor toxin-antitoxin (TA) systems, in which a bacterial toxin lies dormant under normal conditions, prevented from being active by its antitoxin counterpart. As long as the antitoxin is present, the bacterium can continue to exist and is not affected by the TA system. Under conditions of stress, however, the antitoxin is degraded, freeing the toxin to attack its host from within. Although the family of zeta toxins was discovered almost 20 years ago, their deadly mechanism has been enigmatic until now.

The first author on the paper, Hannes Mutschler, and his colleagues studied the molecular mechanism of action of the zeta toxin PezT from the PezAT (Pneumococcal epsilon zeta Antitoxin Toxin) system using the model bacterium Escherichia coli. The PezAT system is found in the major human pathogen Streptococcus pneumoniae—a bacterium that causes serious infections such as pneumonia, septicaemia and meningitis. Bacterial cells in which PezT was activated showed symptoms of poisoning similar to the effects of penicillin. This involved first stalling in the middle of their division stage, and later the intersection zone between the two cell bodies burst and the cells died. The team showed that PezT and other zeta toxins are novel enzymes that transform the essential sugar building block UNAG (UDP-N-acetylg glucosamine) into a toxic molecule. This molecule (UNAG-3P) inhibits the growth of the bacterial cell wall, causing the cells to burst and die.

The findings also enabled the scientists to explain a hitherto paradoxical phenomenon; namely, that the supposedly lethal activity of pneumococcal zeta toxin PezT can eventually boost the pneumococcal infection rate of the entire attacking cellular population. The activation of PezT actively causes individual bacteria to burst and release their cell contents. However, other individuals, which are metabolically less active, can survive the toxin’s activity to some extent. In this process, the accelerated release of bacterial venoms by a subpopulation supports the surviving cells in their attack on the immune system during
infection. It therefore seems that individual pneumococci altruistically sacrifice themselves during infection for the good of the overall population.

"UNAG-3P is a valuable lead-compound for the development of new broad-band antibiotics," says Meinhart, "since it will kill most rapidly growing bacteria." Thus, knowledge of the mechanism of zeta toxins could bring research on antibiotics a major step forward in the battle against bacterial resistance.

**Journal Reference:**

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**National Organization Adds Voice Against HIV-Specific Criminal Laws**

*Micigan Messenger*, (03.15.2011) Todd A. Heywood

The National Alliance of State & Territorial AIDS Directors (NASTAD) is voicing its opposition to the HIV-specific criminal laws on the books in 34 states and two US territories.

"HIV criminalization has often resulted in egregious human rights violations, including harsh sentencing for behaviors that pose little to no risk of HIV transmission," said a statement by NASTAD, which is composed of top state and territory public health officials who are tasked with addressing the epidemic.

NASTAD said that as a member of the Positive Justice Project, initiated by the Center for HIV Law & Policy (CHLP), it is committed to the following:

- Supporting HIV testing and medical record confidentiality as a way to encourage testing and treatment efforts.
- Identifying and sharing best practices related to successes in repealing criminalization laws that are not grounded in public health science.
- Promoting public education and understanding of the stigma and negative health consequences of criminalization laws and prosecutions.
- Providing strong public health leadership on the relative transmission risks and the dangers that punitive responses pose to the epidemic.

NASTAD's members "are the public health professionals who are close to the epidemic, and they know first-hand how powerless stigma drives HIV transmission, and they recognize how HIV criminalization drives stigma," said Sean Strub, the founding publisher of POZ magazine and senior fellow at CHLP. "Their statement will send a powerful message to legislators, prosecutors and others who, whether out of ignorance, fear, ambition or vengeance, promote HIV criminalization."


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**Taylor Was Early and Tireless AIDS/HIV Advocate**

*Associated Press*, (03.23.2011) Sandy Cohen

The HIV/AIDS community is mourning Wednesday’s passing of Elizabeth Taylor, who was as well known for her work on the epidemic as she was for her acting.

Taylor co-founded the American Foundation for AIDS Research (amfAR), which has funneled more than $300 million toward related research. In 1991, the actress started the Elizabeth Taylor AIDS Foundation, which has distributed more than $12 million to US organizations that provide direct care and services to people with AIDS.

"She was profoundly instrumental in helping us identify the resources which have led to the research that has improved and extended the lives of those with HIV and AIDS," said Kevin Robert Frost, CEO of amfAR.

"There have been a lot of incredible warriors in the fight, but she will stand for history on a podium above everyone else," said Craig Thompson, executive director of AIDS Project Los Angeles, a group that benefited from Taylor’s early support.

When Taylor came to Capitol Hill in the early 1990s to testify about AIDS, “Every senator showed up,” Thompson said. “Because Elizabeth Taylor was talking about it, people like my mother were reading about HIV and AIDS.”

“At a time when most Americans thought of HIV/AIDS as something that didn’t affect them, her commitment to the issue and considerable star power helped to take the fight against HIV/AIDS right into the mainstream of American society,” said Don Blanchon, head of the D.C.-based Whitman-Walker Clinic, which named its central facility after Taylor.
“She earned our adoration for her stunning beauty and for being the very essence of glamorous movie stardom,” said AIDS advocate and entertainer Elton John. “And she earned our enduring love and respect for her compassion and her courage in standing up and speaking out about AIDS when others preferred to bury their heads in the sand.”

Sexual Risk Behaviors Among Teens at an Urban Emergency Department: Relationship with Violent Behaviors and Substance Use
Journal of Adolescent Health Vol. 48; No. 3: P. 303-305, (03..2011) Maureen A. Walton, MPH, PhD; Stella Resko, PhD; Lauren Whiteside, MD; Stephen T. Chermack, PhD; Marc Zimmerman, PhD; Rebecca M. Cunningham, MD
Noting that “data regarding sexual risk behaviors among adolescent patients presenting to urban emergency departments (EDs) are lacking,” the authors undertook a study of the rates and correlates of these behaviors among youths screened in an urban ED.

During a one-year period, 1,576 patients ages 14-18 (57.6 percent female, 59.3 percent African-American) completed a self-administered computerized survey. Among the 60 percent who reported being sexually active, 12 percent reported four or more partners. Of these, 45.3 percent reported consistent condom use, and 14.7 percent reported consistent substance use prior to sex.

Regression analyses were used to examine correlates of sexual risk behaviors on the basis of demographics, violence, and substance use. Adolescents with poor grades were more likely to have had sex and have used substances before sex, and were less likely to report condom use. Participants reporting dating violence were more likely to have had sex and less likely to have used condoms, while youths reporting peer violence and weapon carriage were more likely to report substance use prior to sex. Binge drinking and marijuana use were associated with all sexual risk behaviors.

“The visit to an urban ED may provide an opportunity to deliver interventions to address sexual risk behaviors among adolescents,” the authors concluded.

Glimpse of How the ‘Code’ of Life May Have Emerged
ScienceDaily (Mar. 23, 2011) — A portion of the "code" of life has been unraveled by a UC Santa Barbara graduate student from the town of Jojutla, Mexico. Annia Rodriguez worked with John Perona, professor in UCSB's Department of Chemistry and Biochemistry, to decipher intramolecular communication within a large RNA-protein enzyme responsible for expressing the genetic code for the amino acid glutamine. To their surprise, the experiments by Rodriguez captured a partial glimpse of how the genetic coding of life may have emerged.

The results of the study are published in the journal Structure.

Life is based on the ability of all living cells to convert the genetic information in DNA, into the specific sequences of amino acids that make up the proteins that are the cell's workhorses. The key reaction in this decoding process is the attachment of a particular amino acid to one end of a small RNA molecule known as a transfer RNA. The enzyme that catalyzes this amino acid-RNA attachment is the aminoacyl-tRNA synthetase.

Rodriguez performed many laborious experiments in which she removed portions of the aminoacyl-tRNA synthetase that interact with the anticodon stem of the transfer RNA, far from the part of the enzyme that binds the amino acid. Using a biochemical approach known as rapid chemical quench kinetics, Rodriguez discovered that when she made these changes to the enzyme, the binding of the amino acid to the protein was strengthened, even though the amino acid binds far away from the positions where the changes were made.

"It is totally counterintuitive," said Perona. "Imagine if you had a car, and you took out a gear, and the car went faster. Why would you want that gear if it makes your car go slower?"

In all, Rodriguez found that separately removing seven different "gears" from a distant part of the molecule each caused the amino acid to bind more tightly to the aminoacyl-tRNA synthetase. Perona
explained that this provides the first systematic analysis demonstrating long-range communication in an enzyme that depends on RNA for its function.

"So what we think is going on is that these enzyme-RNA interactions far from the amino acid binding site evolved together with the needs of the cell to respond to subtle cues from its environment—especially in terms of how much amino acid is available," said Perona. "It makes sense in terms of evolution."

Rodriguez is the first in her family to pursue a Ph.D., which she will complete this year. Now 28 years old, she began her career as a nurse in Cuernavaca, Mexico. Then she went on to obtain a B.S. in biochemical engineering at the Instituto Tecnológico de Zacatepec.

Graduation from her undergraduate program called for work at a research institution and she chose UCSB.

Although her current research is not focused specifically on human health, Rodriguez said: "My interest in biochemistry started because I wanted to know the mechanisms by which drugs and medications worked inside the human body. I wanted to learn not just the signs and symptoms of disease, but how diseases are developed in a molecular level."

Journal Reference:

'Knowing It in Your Gut': Cross-Talk Between Human Gut Bacteria and Brain

ScienceDaily (Mar. 23, 2011) — A lot of chatter goes on inside each one of us and not all of it happens between our ears. Researchers at McMaster University discovered that the "cross-talk" between bacteria in our gut and our brain plays an important role in the development of psychiatric illness, intestinal diseases and probably other health problems as well including obesity.

"The wave of the future is full of opportunity as we think about how microbiota or bacteria influence the brain and how the bi-directional communication of the body and the brain influence metabolic disorders, such as obesity and diabetes," says Jane Foster, associate professor in the Department of Psychiatry and Behavioural Neurosciences of the Michael G. DeGroote School of Medicine.

Using germ-free mice, Foster's research shows gut bacteria influences how the brain is wired for learning and memory. The research paper has been published in the March issue of the science journal *Neurogastroenterology and Motility.*

The study's results show that genes linked to learning and memory are altered in germ-free mice and, in particular, they are altered in one of the key brain regions for learning and memory—the hippocampus.

"The take-home message is that gut bacteria influences anxiety-like behavior through alterations in the way the brain is wired," said Foster.

Foster's laboratory is located in the Brain–Body Institute, a joint research initiative of McMaster University and St. Joseph's Healthcare in Hamilton. The institute was created to advance understanding of the relationship between the brain, nervous system and bodily disorders.

"We have a hypothesis in my lab that the state of your immune system and your gut bacteria—which are in constant communication—influences your personality," Foster said.

She said psychiatrists, in particular, are interested in her research because of the problems of side effects with current drug therapy.

"The idea behind this research is to see if it's possible to develop new therapies which could target the body, free of complications related to getting into the brain," Foster said. "We need novel targets that take a different approach than what is currently on the market for psychiatric illness. Those targets could be the immune system, your gut function...we could even use the body to screen patients to say what drugs might work better in their brain."

Journal Reference:

Epigenomic Findings Illuminate Veiled Variants: Study Assigns Meaning to Regions Beyond Genes With Implications for Studies of Common Diseases

ScienceDaily (Mar. 24, 2011) — Genes make up only a tiny percentage of the human genome. The rest, which has remained measurable but mysterious, may hold vital clues about the genetic origins of disease. Using a new mapping strategy, a collaborative team led by researchers at the Broad Institute of MIT and Harvard, Massachusetts General Hospital (MGH), and MIT has begun to assign meaning to the regions
beyond our genes and has revealed how minute changes in these regions might be connected to common diseases.

The researchers' findings appear in the March 23 advance online issue of *Nature*.

The results have implications for interpreting genome-wide association studies—large-scale studies of hundreds or thousands of people in which scientists look across the genome for single "letter" changes or SNPs (single nucleotide polymorphisms) that influence the risk of developing a particular disease. The majority of SNPs associated with disease reside outside of genes and until now, very little was known about the functions of most of them.

"Our ultimate goal is to figure out how our genome dictates our biology," said co-senior author Manolis Kellis, a Broad associate member and associate professor of computer science at MIT. "But 98.5 percent of the genome is non-protein coding, and those non-coding regions are generally devoid of annotation."

The term "epigenome" refers to a layer of chemical information on top of the genetic code, which helps determine when and where (and in what types of cells) genes will be active. This layer of information consists of chemical modifications, or "chromatin marks," that appear across the genetic landscape of every cell, and can differ dramatically between cell types.

In a previous study, the authors showed that specific combinations of these chromatin marks (known as "chromatin states") can be used to annotate parts of the genome—namely to attach biological meaning to the stretches of As, Cs, Ts, and Gs that compose our DNA. However, many questions remained about how these annotations differ between cell types, and what these differences can reveal about human biology.

In the current study, the researchers mapped chromatin marks in nine different kinds of cells, including blood cells, liver cancer cells, skin cells, and embryonic cells. By looking at the chemical marks, the researchers were able to create maps showing the locations of key control elements in each cell type. The researchers then asked how chromatin marks change across cell types, and looked for matching patterns of activity between controlling elements and the expression of neighboring genes.

"We first annotated the elements and figured out which cell types they are active in," said co-senior author Bradley Bernstein, a Broad senior associate member and Harvard Medical School (HMS) associate professor at Massachusetts General Hospital (MGH). "We could then begin to link the elements and put together a regulatory network."

Having pieced together these networks connecting non-coding regions of the genome to the genes they control, the researchers could begin to interpret data from disease studies. The team studied a large compendium of genome-wide association studies (GWAS), looking to characterize non-coding SNPs associated with control regions in specific cell types.

"Across 10 association studies of various human diseases, we found a striking overlap between previously uncharacterized SNPs and the control region annotations in specific cell types," said Kellis. "This suggests that these DNA changes are disrupting important regulatory elements and thus play a role in disease biology."

The researchers confirmed the reliability of their approach by showing that SNPs were associated with the appropriate cell types. For example, SNPs from autoimmune diseases such as rheumatoid arthritis and lupus sit in regions that are only active in immune cells, and SNPs associated with cholesterol and metabolic disease sit in regions active in liver cells. While more in-depth, follow-up studies will be needed to confirm the biological significance of these connections, the current study can help guide the direction of these investigations.

"GWAS has identified hundreds of non-coding regions of the genome that influence human disease, but a major barrier to progress is that we remain quite ignorant of the functions of these non-coding regions," said David Altshuler, deputy director at the Broad and an HMS professor at MGH, who was not involved in the study. "This remarkable and much-needed resource is a major step forward in helping researchers address that challenge."

SNPs in the non-coding regions of the genome may have subtler biological effects than their counterparts that arise in genes because they can influence how much protein is produced. The researchers mainly focused on SNPs in enhancer regions, which help boost a gene's expression, and their network connections to regulators that control them and genes that they target. Follow-up efforts can then focus on specific pieces of this network that could be targeted with drugs.

The team involved in this study hopes to expand its analysis to include many other cell types and map additional marks to expand their networks beyond enhancer regions. In the meantime, researchers
involved in genome-wide association studies will be able to use the maps from this project to analyze non-coding SNPs in a new light.

"These maps can be used to come up with hypotheses about how the variants themselves are working and which ones are causal," said Bernstein. "This resource now goes back to the GWAS community, which can use the maps to form and test new functional models."

**Journal Reference:**

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**Gay men reduce their risk behaviour after HIV diagnosis, studies find, but disagree on how much by**
Gus Cairns
Published: 25 March 2011

Two studies presented at last month’s 18th Conference on Retroviruses both found that gay men diagnosed with HIV considerably reduce the amount of sex they have that could pass on their infection. However the two studies disagreed on how much men reduced their risk behaviour, and for how long they sustained this reduction.

The two prospective cohort studies, from Amsterdam and San Francisco, did not look at gay men’s behaviour over the same time frames so cannot be directly compared.

The Amsterdam study followed a group of 206 initially HIV-negative gay men and monitored the sexual risk behaviour of those who acquired HIV from four years before the date of diagnosis to four years afterwards. They were thus able to determine what the men’s baseline behaviour had been before diagnosis.

As a long-established cohort, it was also able to compare the behaviour of men diagnosed before HIV combination therapy came along (1984-1995) and after (1996-2008).

The San Francisco study only followed the risk behaviour of its 237 subjects from the date of diagnosis, but followed behaviour out to twelve years after diagnosis.

In addition, while the Amsterdam study only monitored the prevalence in unprotected anal intercourse (UAI) regardless of partners’ HIV status, the San Francisco study looked at rates of anal intercourse (AI) with all partners and partners of negative or unknown HIV status as well as rates of unprotected *insertive* anal intercourse (UIAI – the kind of sex most likely to transmit HIV) with partners of known and unknown status.

It also conducted a second analysis in which it took account of the effect of viral suppression by regarding unprotected sex by men with viral loads below 500 copies/ml as representing zero risk of transmission.

**Amsterdam**
In Amsterdam, it was found that HIV diagnosis produced an immediate fall in the amount of unprotected anal intercourse men had. Before diagnosis 68% of men had had UAI (defined as “not (always) using a condom during anal sex”) in the previous year. One year after diagnosis this had reduced to 38% and thereafter the proportion of men who had UAI continued to decline more slowly: four years after diagnosis it was 32%.

In the post-HAART era, however, post-diagnosis UAI rates decreased a lot less and started to increase again after the first post-diagnosis year. The proportion of men who had had UAI in the previous year was 61% four years before diagnosis, 72% at diagnosis, 53% one year post-diagnosis, then back to 61% four years after diagnosis.

**San Francisco**
The San Francisco study presented an apparently very different pattern of behaviour. This study counted the number of partners men had had in the previous three months. This was ten at diagnosis but then declined to seven two years after diagnosis. It then increased again to 8.5 five years after diagnosis and then declined again, reaching 3.5 ten years after diagnosis.

This absolute decline in the number of partners could be accounted for by age and the acquisition of primary partners, but it was notable that the proportion of sex with partners of negative or unknown HIV status followed a similar pattern of initial decline, then resurgence, then final decline. At diagnosis the men in the study had averaged six partners in the last three months of negative or unknown HIV status (60% of all partners); two years after diagnosis it was 2.5 partners (36% of all partners); five years after diagnosis it was back to 6.25 partners (69% of all partners), but by year ten it was down to one partner (29% of all partners).
Note that this was all anal sex, protected or not. In the case of unprotected insertive anal sex (UIAI, the behaviour most likely to pass on HIV) it declined from four UIAI partners in the last three months at baseline to one five years after diagnosis, and then very slowly increased to 1.5 at year ten. The proportion of insertive sex that was unprotected became larger than the proportion with negative or unknown-status partners nine years after diagnosis, perhaps indicating that by this time the majority of men were only having UIAI with other men known to have HIV.

The majority of UIAI was with other HIV-positive partners throughout. The number of partners of negative or unknown status with whom the men had UIAI declined from 1.8 in the last three months at baseline to 0.57 after a year and was only 0.14 after five years.

The researchers calculated that even without taking viral suppression into account, this meant that the San Francisco men reduced the risk of their passing on HIV by 71% a year after diagnosis, 87% two years after diagnosis, and 92% five years after. If the proportion with viral loads under 500 was taken into account, then gay men reduced their chance of passing on HIV by 97% after two years and maintained that reduction in risk.

**Comparing the two**

It’s difficult to compare the two studies directly because there is not one single measure they use in common. The proportion of men in the Amsterdam study who had unprotected anal sex in the post-HAART era only declined by 20% a year after their HIV diagnosis, whereas the San Francisco men had reduced the amount of *insertive* unprotected sex they had by nearly 50% at this point. They had reduced UIAI by 75% four years after diagnosis, by which time the UAI levels in Amsterdam men were back almost to baseline.

These figures do not, however, take account of the possibility of “strategic positioning”: the San Francisco men might be having a higher proportion of sex that was unprotected, including with negative or unknown-status partners, if, post-diagnosis, the majority of that sex was as the passive partner. We can’t tell from this study.

It is noticeable that, in the San Francisco study at least, the majority of the reduction in the risk of transmission was due to behaviour change, rather than the reduction in infectiousness due to decreased viral load.

**References**


**Fertility treatment can use semen from men with HIV**

By Genevra Pittman

NEW YORK | Thu Mar 24, 2011 1:21pm EDT

(Reuters Health)—Fertility treatments can be done safely and effectively in couples where the man is infected with the AIDS virus and the woman isn’t, according to a new review of past studies.

Over the last 2 decades, researchers have improved methods of "washing" the semen of men infected with HIV, the virus that causes AIDS. Unwashed semen could pass HIV to the woman or their baby.

"I think the procedure is getting safer and safer," said Dr. Deborah Anderson, a scientist at the Boston University School of Medicine who studies HIV. She was not involved in the current research, but she told Reuters Health that washing the man’s semen lowers the risk of transmission enough that "it’s an acceptable ... procedure for couples that really want to have children."

In the new review, published in the journal Fertility and Sterility, researchers from the Evandro Chagas Clinical Research Institute in Rio de Janeiro, Brazil looked at 17 earlier studies involving a total of about 1,800 couples in which only the male partner had HIV.

In each of the studies, researchers performed one of two common types of fertility treatments after washing the semen. Then they recorded how often women became pregnant after the procedures. They also monitored the women and any babies they had as a result of the procedures, to see whether HIV had been passed on from the semen.

About a third of the women had a procedure in which a single sperm is injected into a single egg; then the fertilized egg is placed into the woman’s womb. This kind of fertility treatment is assumed to be safer for couples in which the male partner has HIV because it is easier to ensure that the sperm being used does not have the HIV virus.
The rest of the women had sperm injected directly into the womb, when their eggs were most likely to be there.

Ultimately, roughly half the women became pregnant, and about 80 to 85 percent of the pregnancies resulted in the birth of a baby.

The success rates for pregnancy were comparable to what has been shown in other studies of fertility treatment in couples without HIV. If anything, couples in the current study may have been more likely to get pregnant using fertility treatments because many of them had no underlying fertility problems, the authors say.

None of the women in the study, or babies that were born after fertility treatments, tested positive for HIV. However, in a few of the studies in which researchers tested semen after it was washed, between two and eight of every 100 samples tested positive for HIV—indicating that it still may be possible, if unlikely, for the virus to be passed either to the woman or to the fetus.

However, the findings are "very reassuring," according to Dr. Elizabeth Ginsburg of the Brigham and Women’s Hospital Center for Reproductive Medicine in Boston.

Ginsburg, who was not involved in the study, said that even if some of the samples did test positive for HIV, the amount of the virus was probably so small that it wasn't likely to be passed to the mother or baby. In addition, she said, HIV transmission requires some sort of trauma to the woman's body because the virus is passed from semen to blood, and although there's a chance of that in intercourse, it's not likely in fertility treatment.

Despite mounting evidence of its safety, fertility procedures are not very common in couples in which the male partner has HIV. In part that's because the procedures aren't often covered by insurance, Ginsburg said. Although some fertility procedures may be as inexpensive as $1,000, others run many times higher.

"One of the things that is a shame is that when couples can't afford fertility treatment, they're stuck with the other option, which is having timed intercourse, and that puts the woman at risk," Ginsburg said.

Anderson said a new option for these couples might become available in the future—medications that the woman can take to avoid getting the virus from her partner who has HIV. And, "if the mom doesn't get it, the baby's not going to get it," she said. "I think that's going to be the future of this field."

So far, only a couple of early studies have been done on the drugs' effectiveness at preventing transmission of the virus, and for now, Anderson said, fertility treatment is the safest possible option for these couples.

**Glaxo Accuses Abbott of Stifling Competition on AIDS Drug**

*By Pamela MacLean and Karen Gullo—Mar 24, 2011 3:31 PM ET*

A GlaxoSmithKline Plc (GSK) lawyer told a federal court jury that Abbott Laboratories sought to stifle competition and maintain an illegal monopoly over HIV drugs when it quadrupled the price of its AIDS medicine Norvir in 2003.

Glaxo has argued at a trial in Oakland, California, that the price increase meant that other drugmakers couldn’t compete with Abbott’s Kaletra AIDS medicine, which includes Norvir, a boosting agent for other HIV drugs.

The London-based drugmaker claims it lost an estimated $570 million in profit on sales of its drug Lexiva, which uses Norvir, because it sold at half the rate the company expected. Glaxo is seeking damages of about three times its lost profits on Lexiva.

"This was about money for Abbott and they wanted to make sure Kaletra stayed on top,” Brian Hennigan, Glaxo’s lawyer, said today in his closing argument.

Abbott says it increased Norvir’s prices for legitimate business purposes. Even with the higher price, Kaletra lost market share and had only 30 percent of the market for similar drugs, the company has said.

Abbott increased the wholesale price of a Norvir capsule containing 100 milligrams from $1.71 to $8.57, the Abbott Park, Illinois-based company said in court documents.

James Hurst, Abbott’s attorney, told jurors today in his closing that the company raised the price of Norvir “to make more on Norvir” because of the introduction in 2003 of a competing Bristol-Myers Squibb drug, Reyataz, that needed just one Norvir tablet, rather than four.

“That explains the price increase,” he said. “It was a different use, so it needed a different price.”

**‘Still the Lowest’**

Norvir went from the lowest-priced HIV drug “on the market by far to still the lowest even after the price increase,” he said.
Abbott settled claims by retailers including Rite Aid Corp. (RAD) and Safeway Inc. for an undisclosed amount, Adelle Infante, a company spokeswoman, said today in an e-mail. The drug retailers and other direct purchasers had also sued Abbott, claiming its conduct drove up prices for medicines that compete with Kaletra.

The drug retailers sought damages equal to triple the $1 billion in alleged overcharges. Terms of the agreement will be made public when they are filed in court, Infante said.

In 2009, a federal appeals court in San Francisco ruled that Abbott’s pricing for the HIV drugs wasn’t unlawful because Kaletra wasn’t priced below its cost. In 2008, Abbott settled a similar antitrust lawsuit filed by patient groups for $10 million.

The case is SmithKline Beecham Corp. v. Abbott Laboratories (ABT), 07-5702, U.S. District Court, Northern District of California (Oakland).

**Improving Adherence and Clinical Outcomes Through an HIV Pharmacist's Interventions**

_AIDS Care Vol. 22; No. 10: P. 1189-94, (10..2010)  Angela Ma; David M. Chen; Fern M. Chau; Parya Saberi_

The assistance of an HIV clinical pharmacist can benefit patients in terms of regimen complexity, adherence and immunologic and virologic outcomes, the authors of the current study report.

Though antiretroviral therapy (ART) can effectively suppress HIV and boost immunologic response, most patients struggle with adherence, the authors noted. While previous studies showed that clinical pharmacists contribute to management of HIV patients, variability in the pharmacist’s responsibilities and study limitations have hampered a thorough evaluation.

In this retrospective study, an HIV clinical pharmacist’s interventions included suggesting regimens to suppress HIV, improve immunologic response, minimize adverse events, and optimize adherence by reducing pill burden and/or dosing frequency. Ma and colleagues assessed the efficacy of these interventions on pill burden, frequency, adherence, and patient clinical outcomes. The study took place at the Kaiser Permanente Medical Care Program, Vallejo, Calif., from September 2006 to September 2008.

From a cohort of 75 patients, mean daily pill number and dosing decreased from 7.2 pills/day and 2.0 times a day in the control phase to 5.4 pills/day and 1.5 times/day during the study, respectively (p<0.001.) Adherence increased from a mean of 81 percent to 89 percent (p=0.003).

“Clinical outcomes measured by CD4+ cell count and CD4 percent were statistically improved, and more individuals achieved undetectable HIV viral loads post-intervention (p<0.001),” the authors found.

“In conclusion, HIV clinical pharmacists may play an important role in reducing pill burden and dosing frequency, increasing medication adherence, and improving clinical outcomes.”

**Do Black Patients Respond Less Well to Antiretroviral Therapy?**

**SUMMARY:** African-Americans had a 40% greater likelihood of virological failure on antiretroviral therapy even after controlling for known risk factors, according to a meta-analysis of ACTG trials presented at CROI 2011.

_by Liz Highleyman_

Several studies over the course of the HIV/AIDS epidemic have found that blacks (and perhaps also Hispanics/Latinos) do not respond as well as whites to antiretroviral therapy (ART).

Some analyses have indicated that this disparity is attributable to socio-demographic factors and less access to care, but others suggest such differences remain even when researchers try to control for these factors.

At the 18th Conference on Retroviruses and Opportunistic Infections (CROI 2011) this month in Boston, Heather Ribaudo from Harvard School of Public Health presented findings from an analysis of racial differences in treatment response among participants in 5 studies conducted by the AIDS Clinical Trials Group (ACTG) between 1998 and 2005.

The analysis included 2495 previously untreated non-Hispanic white (n = 1344) and black (n = 1151) participants who initiated ART in these 5 trials. Studies were mostly done in the U.S. and each included 30%-40% black enrollees. Most participants (about 80%) were men and the average age was 37 years. About two-thirds used 3-drug ART regimens containing 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus either an NNRTI or a protease inhibitor.
Ribaudo and colleagues looked at rates of virological failure, or inability to achieve and maintain undetectable viral load on combination ART, after adjusting for a variety of factors thought to influence treatment response, including age, sex, disease status, comorbidities, mode of HIV transmission, depression, education level, alcohol use, “self-efficacy,” and perceived social support.

**Results**

- Overall, 45% of black participants and 32% of white participants experience virological failure, defined as viral load > 1000 copies/mL at week 16-24 or > 200 copies/mL after 24 weeks.
- In an intent-to-treat analysis, black participants had a significantly higher risk of virological failure compared with white patients (hazard ratio 1.6, or 60% greater risk).
- This difference was consistent across different types of ART regimens.
- The difference was reduced after adjusting for known potential confounders, but blacks still had a significant 40% higher risk of virological failure (hazard ratio 1.4).
- Results were similar in an as-treated analysis looking at actual—rather than assigned or intended—treatment regimen.
- In addition to race, other factors associated with increased risk of virological failure included:
  - Younger age;
  - Lower baseline CD4 T-cell count;
  - Higher baseline HIV RNA level;
  - Less education;
  - Hepatitis C coinfection;
  - Recent non-adherence.
- Unlike some past studies, this analysis saw no association between virological failure and sex or alcohol use.
- Despite increased risk of virological failure, however, black participants showed greater CD4 cell gains over 96 weeks (though not at 24 or 48 weeks).
- After adjusting for other factors including baseline CD4 count, blacks gained an average 33 cells/mm3 more than white participants.

Based on these data, the researchers concluded, “In these ACTG studies, black race was associated with a 40% higher risk of virological failure on initial ART regimens than white race.”

“Two finding did not appear to be explained by recent adherence and potential confounding demographic, medical, or social factors that were measured,” they continued.

At a CROI press conference Ribaudo noted that link between black race and poorer treatment response was “very robust” and “very consistent,” even when attempting to control for factors associated with treatment access. However, she noted, this analysis was not able to address all factors related to access to care, nor did it analyze genetic differences.

“We were not able to capture some key social factors that might be a measure of more challenging life situations that patients might face, such as housing status, income level, and the number of dependents in a family,” Ribaudo said.

Differences in virological failure rates were observed across a broad range of regimens, making it less likely that differences are due to pharmacogenetic associations, she added. 3/25/11

**Reference**


**Cruise Ship Norovirus Outbreak Highlights How Infections Spread**

ScienceDaily (Mar. 25, 2011) — Norovirus is the leading cause of acute gastroenteritis in the United States and is estimated to cause nearly 21 million cases annually. It is highly transmissible through person-to-
person contact and contaminated food, water, and environmental surfaces. The results of an investigation of a 2009 outbreak on a cruise ship shed light on how the infections can spread and the steps both passengers and crew can take to prevent them.

The findings are published in a new study in *Clinical Infectious Diseases*. Questionnaires about when people did or did not seek medical care, hygiene practices, and possible norovirus exposure were placed in every cabin after the outbreak began. The ship had 1,842 passengers on board, and 83 percent returned the questionnaires. Of the 15 percent of respondents who met the case definition for acute gastroenteritis, only 60 percent had sought medical care on the ship. Infected passengers were significantly more likely to have an ill cabin mate and to have resided or dined on the deck level where a vomiting incident had occurred during boarding. The most common symptom reported was diarrhea, followed by vomiting. Stool samples from several ill passengers tested positive for norovirus.

Less than 1 percent of the crew reported illness, and their low attack rate may have been due to the few crew members who had direct contact with passengers. This included separate sleeping and dining areas and alternate passages for boarding and exiting the ship. Another factor may have been an acquired short-term immunity from previous cruise ship outbreaks.

"Cruise line personnel should discourage ill passengers from boarding their ships," according to study author Mary Wikswo, MPH, of the Centers for Disease Control and Prevention. "Once on board, passengers and crew who become ill should report to the ship's medical center as soon as possible. These quick actions are crucial in preventing the introduction and spread of norovirus on cruise ships and allow ship personnel to take immediate steps to prevent the spread of illness."

**Journal Reference:**

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**MRSA Infection Shown to Be Seasonal**

ScienceDaily (Mar. 24, 2011) — A new study from Rhode Island Hospital has found a significant increase in the occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the summer and autumn months. The increase was more pronounced in the pediatric population than in adults. The study is now published online in advance of print in *PloS ONE*.

Lead author Leonard Mermel, D.O., Sc.M., medical director of the department of epidemiology and infection control at Rhode Island Hospital, and his colleagues conducted a retrospective 10-year study by examining MRSA isolates submitted to the hospital's microbiology laboratory.

Their findings indicate that for pediatric patients there were approximately 1.85 times as many community-associated (CA) MRSA infections and 2.94 as many hospital-associated (HA) MRSA infections in the third and fourth quarters of the year than in the first two quarters. For adults, there were 1.14 times as many CA-MRSA infections in the second two quarters as in the first two quarters, but no seasonal variation was observed in adult HA-MRSA infections.

The researchers also reviewed published articles over the last 70 years that had any mention of seasonality and *Staph aureus* infections. They summarized the literature search in two comprehensive tables that reveal an increased incidence of such infections during summer and autumn in many temperate regions of the world and during the warmest months of the year in tropical regions.

The researchers believe that it is the sequence of the third and fourth quarters that is important in demonstrating the peak in MRSA infections rather than just the warmest quarter of the year. Mermel says, "We reviewed meteorological data for Rhode Island during the decade of our study period and found that the second quarter was warmer, on average, than the fourth quarter. We believe that an increased incidence of infection in autumn, the fourth quarter, may reflect a lag between Staphylococcal colonization and subsequent infection."

The researchers note that hydration of the skin is important for microbial growth, and maximum hydration is achieved when high temperatures combine with high relative humidity, which also promotes increased sweat production. Mermel says, "The presence of both factors, heat and humidity, may be critically important in providing the environmental conditions that facilitate heavy grown of *S. aureus* on the skin."

Mermel, who is also a professor of medicine at The Warren Alpert Medical School of Brown University, says, "We've demonstrated that Staph infections, particularly skin infections in children, follow a seasonal pattern. Until now, this basic observation of one of the most common human infections
has been generally unnoticed, minimized or doubted in the medical literature." He concludes, "It is hoped that this study will promote further investigation into the seasonality of S. aureus infections to better understand the biologic basis for this observation."

**Journal Reference:**
DOI: 10.1371/journal.pone.0017925

**Study Reports High Rate of Selection for Lamivudine Mutations in HIV-Infected, Treatment-Naive Children at the Time of Virologic Failure**

“We included all the human immunodeficiency virus (HIV) type 1-infected highly active antiretroviral therapy (HAART)-naive children who started an LPV/r-based regimen between 2000 and 2009 at the Necker Hospital (Paris, France). Virologic failure (VF) was defined as an HIV-RNA ≥50 copies/mL. Resistance genotypic test was performed in case of VF. ...

“HAART included LPV/r and 2 nucleoside reverse-transcriptase inhibitors, mainly lamivudine (3TC), zidovudine, and/or abacavir. ... Less than 50 copies/mL of HIV RNA was observed in 46%, 67%, and 70% of the children at months 6, 9, and 12, respectively. In all, 20 children (46.5%) experienced a VF. The risk factors of primary VF were a young age and a low socioeconomic status. The genotypic resistance test, performed for 18 of 20 children with VF, revealed 1 LPV/r-resistant virus and protease inhibitor-related major mutations without LPV/r resistance in 2 other children. Of the 18 children with VF, 15 received a 3TC-based HAART: 12 of 15 (80%) harbored a 3TC-resistant virus. No virus resistant to zidovudine or abacavir was found. ...

“ ... In all, 70% of HAART-naive children had virologic success at month 12. The selection of LPV-resistant strains was a rare event. A high rate of selection of 3TC-mutations strengthens the recommendation to prefer a first-line 3TC-sparing regimen, particularly for children with risk factors of poor adherence.”

By Richard P. Grant

**Mitotic Hijacker**

When a cell divides, its duplicated chromosomes have to be shared equally between the two daughter cells. Cells manage this feat by lining up replicated chromosomes along their equators during mitosis, and then pulling sister chromatids apart to the right destinations. But *Theileria*, an intracellular parasitic protozoan, also needs to divide when its host cell undergoes mitosis. Dirk Dobbelaere and colleagues at the University of Bern have now shown how *Theileria* hijacks the host cell’s mitotic machinery to ensure its continued survival (*PLoS Biol, 8:e1000499, 2010)*.

Some species within the genus *Theileria* cause variants of theileriosis, an economically important tick-borne disease that affects cattle in the tropics and subtropics. The parasite infects white blood cells, but unlike the malaria parasite *Plasmodium*, to which it is closely related, *Theileria* dissolves the enclosing membrane soon after infection and takes up residence in the cytoplasm. It rapidly latches onto host microtubules and differentiates, forming a multinucleate mass called a schizont. In this form, *Theileria* performs the trick, unique among eukaryotic parasites, of coaxing the host cell to divide continuously and resist apoptosis. This causes a cancer-like state in the host animal’s tissues which also allows the schizont to proliferate. To maintain the host cells in this transformed state—and to stay alive—the schizont must split itself between daughter cells each time the host cell divides.

Dobbelaere first came across the theileriosis while working as a vet in Zanzibar, 30 years ago. European cattle imported to Zanzibar were rapidly succumbing to the disease. “I arrived just in time to see the last ones die,” he says. As a result, he got involved in a tick-control project to combat East Coast fever, a severe form of theileriosis caused by the species *T. parva*. But rather than trying to fight ticks, he got interested in the parasite itself and moved to the International Laboratory for Research on Animal Diseases (ILRAD) in Nairobi, where he studied *Theileria* for five years.

Dobbelaere left ILRAD with a PhD and eight publications. “I was in a very lucky position, to be able to walk in as a vet and walk out as a researcher,” he says.

It was an old paper in *Nature* (L. Hulliger et al., 203:728-30, 1964) that piqued Dobbelaere’s current interest in the problem of how *Theileria* distributes itself between daughter cells. “I was intrigued by the efficiency of the process,” he says. He was finally able to address the problem when he read a more recent paper that described a highly specific inhibitor of a key mitotic kinase, Polo-like kinase 1 (Plk1).

Dobbelaere’s graduate student, Conrad von Schubert, used this inhibitor, called BI-2536, to perform what F1000 Member Christine Clayton at the University of Heidelberg calls a “very careful inhibitor-
based analysis” of the parasite-microtubule interaction. After observing host Plk1 molecules studding the surface of schizonts during mitosis, von Schubert used BI-2536 to stop the action of Plk1 at precise stages during the cell cycle. This enabled von Schubert and Dobbelaere to build a model of how the parasite interacts with the mitotic apparatus at each stage of cell division.

First, the schizont binds to newly formed microtubules at the spindle poles, spreading itself over the mitotic spindle where the condensed host chromosomes assemble at metaphase. Then, as the sister chromatids are pulled apart at anaphase, the parasite recruits Plk1, which allows it to latch onto the central spindle that forms between the two sets of host chromosomes. Because Plk1 contributes to the control of the cleavage furrow and the contractile ring that eventually separates the two daughter cells, the Plk1-studded schizont attracts the contractile ring to form around its own middle, squeezing it in half and dividing it equally between the two new cells. Critically, von Schubert was able to shut down Plk1 activity at anaphase using BI-2536, with the result that as the host-cell contractile ring closed, the parasite was confined to just one daughter cell.

Despite these insights, the identity of the molecule on the parasite’s surface responsible for binding Plk1 remains mysterious. Also unknown is how Theileria gets into a host cell in the first place. The parasite doesn’t bind to mouse or human white blood cells, and he would like to find out what bovine receptor is responsible, so the parasite could be studied in better-modeled cells. Additionally, the United States prohibits the import of Theileria, and very few groups worldwide are working on it. Dobbelaere hopes that his paper sparks interest in the parasite, and that more researchers get involved.

**HIJACKER MIOSIS**
by RAVI NAMBY, [Comment posted 2011-03-25 23:05:42]
Aids hiv also attacks white blood corpuscles, and then how to prevent these hijacker miosis parasites. It attacks our defence, then how our defence who can prevent
This parasite, hijacker miosis parasite.

**Changes in gene expression ...**
by ABIZAR A LAKDAWALLA, [Comment posted 2011-03-25 12:17:10]
Would be interesting to perform an RNA-seq experiment on the different stages in infected and non-infected cells to tease apart the genes involved ...

**Brilliant work**
by James Wasmuth, [Comment posted 2011-03-25 11:23:49]
I recall being blown away when I read about how Theileria replicates. As a parasitologist myself, I'm always happy when such major insights into parasite biology and its interaction with the host are uncovered.

**European guidance published on the use of tropism tests in routine HIV care**
Michael Carter
Published: 28 March 2011
Detailed European guidance about the use of tropism testing in routine HIV care has been published in *Lancet Infectious Diseases*.

The consensus statement was drawn up by 60 panellists from 31 countries.

“The European Consensus Group on clinical management of tropism testing provide an overview of available published work, evidence-based recommendations for the clinical use of tropism testing and guidance on unresolved factors and developments,” write the authors.

Viral tropism is the ability of viruses to enter and infect cells, and is based on the ability of viruses to bind to co-receptors on these cells.

HIV uses one of two co-receptors – CCR5 or CXCR4. In most cases, the virus uses CCR5, but CXCR4 virus is found in patients with a low CD4 cell count and in those with extensive experience of HIV treatment.

An antiretroviral drug that targets HIV’s attachment to the CCR5 co-receptor is maraviroc (*Celsentri*). In both Europe and the US, the drug is approved for use of combination HIV therapy by treatment-experienced patients. In the US, but not Europe, it is also licensed for the treatment of antiretroviral-naïve individuals.

However, maraviroc only works if a patient has HIV that uses the CCR5 co-receptor. Therefore, patients must have a tropism test to assess their suitability for treatment with maraviroc.

Guidelines for the use and interpretation of tropism tests are therefore needed. Investigators reviewed the results of 57 published papers and 42 conference abstracts on the use of tropism tests.

All recommendations had the agreement of 75% of the panel, and the strength of the recommendations was graded as strong, moderate and optional.
The panel strongly recommended that a tropism test should be performed in all circumstances before a patient initiated CCR5 inhibitor therapy. Testing was strongly endorsed for individuals for whom a CCR5 inhibitor was being considered after virologic failure with an earlier regimen.

Patients starting HIV therapy for the first time could have a tropism test before initiating therapy if they are considered to have a high risk of side-effects using conventional first-line anti-HIV drugs. The panel recommend that tests should be conducted as soon as possible before treatment is started, but note, “the use of maraviroc in antiretroviral-naïve patients is not approved by the EMA [European Medicines Agency].”

Also contained in the guidelines are recommendations about the type of tropism test to be used. The choice depends on the viral load of a patient.

For patients with a viral load above 1000 copies/ml, tropism testing using either the enhanced sensitivity Trofile assay or V3 loop genetic population analysis received an endorsement of moderate strength.

“The choice of the test should be based on the local capacity, logistics, cost and desired turnaround time,” write the panel.

However, they add, “in general, V3 loop population sequencing is preferred because of its better availability and faster turnaround time. If this method is used, the laboratory should have appropriate expertise in sequencing analysis and use of interpretation techniques and should participate in quality control procedure to validate their accuracy.”

The preferred method of analysis for patients with a viral load between 50 – 1000 copies/ml is the V3 loop. However, the strength of the recommendation was weak.

For patients with an undetectable viral load tropism testing should be done on proviral DNA. Once again, the strength of the recommendation was weak, or optional.

Also in the guidelines are recommendations about the turnaround times for testing.

The importance of speed was emphasised for patients who were possible candidates for CCR5 therapy because of virologic failure. The panel strongly recommended that tropism testing should be performed at the same time as resistance surveillance. “New regimens can therefore be started immediately, avoiding the continuation of failing treatment and associated risk of the accumulation of drug resistance mutations while the tropism test results are awaited.”

Lack of published data prevented the panel from making recommendations about the longevity of test results. However, they suggested that the risk of tropism change was low for patients with higher CD4 cell counts. But the investigators emphasised the need for short turnaround times for individuals with a low CD4 cell count, as well as those taking a failing regimen. “In this case,” they write, “genotypic assays using population sequencing are preferable to phenotypic assays.”

The test report sent by laboratories to doctors should, the guidelines stress, “include clear advice as to whether the tropism result supports the use of a CCR5 antagonist or not.” The guidance also states that the laboratory report should indicate which type of test was used, and that “virologists providing the results should have knowledge of the association between sensitivity and specificity of tropism prediction and cutoff settings.”

The guidelines conclude, “current data lend support to both the use of population genotyping and the commercially available enhanced sensitivity Trofile assay...for practical reasons, genotypic population sequencing is the preferred method in Europe.”

Reference
Vandekerckhove LPR et al. European guidelines on the clinical management of HIV-1 tropism testing. Lancet Infectious Diseases, online advance publication, March 22, 2011. (click here for access to the free abstract).

Dark side of giving: The rise of philanthro-capitalism
Naren Karunakaran, ET Bureau, Mar 25, 2011, 08.16am IST
A few years ago, Paul Kagame, president of Rwanda, had a chance meeting with Som Pal, former member of the Planning Commission and earlier minister of state for agriculture, and was bowled over by his sage-like views on developmental issues. The president promptly invited Som Pal to his blighted country to suggest policy measures to get out of a developmental quagmire. Som Pal travelled to Rwanda; he was hosted at the presidential palace and allocated an entire office during two long stints.

Rwanda was sitting on a food security crisis in spite of having fertile land and favourable climatic conditions. "A set of policy guidelines and an action plan were quickly crafted. I held out a promise to Kagame — Rwanda could be food surplus in a short time,” recalls Som Pal.
His plans were, however, rendered futile, as a hostile system overwhelmed him, even attempting to buy water hand-pumps at $12,500 apiece. "Most African leaders are only keen on projecting the agony of their people for international support in dollars," laments Som Pal. "A complete nexus between institutions, large corporations and narrow, vested interests are at work." Elements of this trend can be seen in India too.

Since then, Som Pal has had several brushes with Kenya and Zambia too; the story runs along similar lines. How then would he evaluate the much celebrated Alliance for a Green Revolution in Africa (AGRA) — an initiative driven by the Rockefeller Foundation and the Bill & Melinda Gates Foundation, the oldest and the largest philanthropic repositories, respectively, in the world? The Gates Foundation alone has committed $264.5 million to AGRA.

"They are using the pitiable condition of the African people to get a foothold into the continent," explains Som Pal. "Their large philanthropic resources are being utilised to further the interests of business." In countries with weak governance mechanisms, like in Africa, it becomes a lot easier.

Proponents of chemical-free and GMO-free (genetically modified organisms), sustainable agricultural practices like Som Pal are beginning to feel uncomfortable about AGRA and a host of big-ticket philanthropic initiatives across developing countries. As are an increasing number of independent policy wonks and scientists across the world.

For instance, the Gates Foundation's sheer clout is taking it, intentionally or unintentionally, to places where policy, business and philanthropy intersect. There are its business and investment links with large companies that are driven by the profit motive. There is its growing stranglehold in the policy-making space across emerging markets, especially in education, healthcare and agriculture.

The $23.1-million investment by the Gates Foundation in Monsanto, the world's largest producer of GM seeds, is a small example of a trend.

Civil society organisations see it as vindication of what they had always suspected: the unstated agenda of pushing GM crops into Africa. In recent times, though, following strident protests, Bill Gates appears to have tempered his views on agriculture; he talks about picking the best from organics and tech-driven agriculture.

The Gates Foundation's insistence that its investments and grants ought to be seen separately has also attracted considerable flak. The question is asked: how can it be a 'passive investor' in companies such as Monsanto when its avowed goal is doing good with philanthropic monies? "Doubts about his (Bill Gates) larger motives, despite some good outcomes of his charity, are beginning to cloud my thinking," concedes Mira Shiva, a public health activist. Two emails sent by ET to the Gates Foundation, on December 29 and March 22, went unanswered.

In his blog postings and writings, Eric Holt-Gimenez, director of the US-based Food First: Institute for Food and Development Policy, labels it 'Monsanto in Gates' clothing'.

He describes how AGRA, as a prelude to the introduction of GMOs, is laying the ground for a conventional breeding programme — labs, experiment stations, agronomists, extensionists, biologists and farmer seeds. He points out that about 80% of the Gates Foundation’s allocation to Kenya has gone into biotech research; in 2008, about 30% of its agri-development funds went into promoting and developing GM seeds.

GRAIN, an international non-profit that supports community-controlled and biodiversity-based food systems, has been wary of public-private coalitions like AGRA and the Consultative Group on International Agricultural Research (CGIAR).

It says their research programmes feed into the growth strategies of corporations; further, the programmes often adopt elements of business models of those very companies. Delhi-based Shalini Bhutani, till recently representing GRAIN, sees a design in the Gates Foundation's announcement of the Borlaug Institute for South Asia in Bihar, following a recent visit by Bill Gates. "The involvement of this set of players in the promotion of GM rice is too well known," she says. AGRA, it is often charged, has been created with little civil society or farmer engagement. Protests are now breaking out across the continent. The Kenya Biodiversity Coalition, with a membership of 65 civil society and farmer organisations, tried to block the import of a 40,000 tonne consignment of GM maize into the country last year.

Food First is concerned that US agencies, acting in tandem with MNCs, are gaining muscle by the day. The Casey-Lugar Global Food Security Act—a legislation that seeks to tie foreign aid to GMOs—is often cited. Or, that the newly appointed head of USAID is a former Gates Foundation employee. A set of powerful voices — in business and in philanthropy — are beginning to talk of a new GM-led green revolution despite the ravages of the previous green revolution techniques, which were grounded in
similar principles, in India. In the Punjab, Haryana and western UP belt, soils are degraded, and yields and groundwater levels are plunging, causing deep socio-economic challenges.

The onslaught continues despite numerous studies indicating that GM crops are no panacea. A few years ago, the International Assessment of Agricultural Knowledge, Science and Technology for Development (IAASTD) — a multi-stakeholder consultation that lasted three years, and involved 900 experts from 110 countries — concluded GM crops are no solution to the world's food security challenges.

**Second Only to the US**

Concerns aired by agriculturists are finding an echo in another arena in which philanthropic capital, in recent years, has catalysed remarkable progress: healthcare.

It has delivered results in access to medicines, research in neglected and tropical diseases, development and distribution of vaccines to low-income countries, maternal, neonatal and child health, and nutrition.

The Gates Foundation and its partners have re-invigorated health issues and given them a global profile like never before. Since 1994, the foundation has invested over $13 billion in healthcare alone, representing 60% of its giving to date.

In public health, other than the US government, there is no donor as influential as the Gates Foundation. It has emerged as the second largest donor to the World Health Organisation (WHO). This can be seen both ways: donor money has infused life into a nearly bankrupt entity, but it is also causing much consternation.

Effects of the structural changes being pushed by the new interests will be seen years or decades down the line.

"The very mandate and constitution of the WHO is being undermined," says KM Gopakumar, legal advisor and senior researcher of the Third World Network in India.

Speaking to the media in Bangalore this week, Warren Buffett, who has committed most of his $50 billion wealth to the Gates Foundation, admitted it takes a long time to see the full results of philanthropic work.

While it is conceded that it would be downright impudent to look a gift horse in the mouth, the concentration of power in the hands of new philanthro-capitalists is causing alarm; especially on issues around equity and social justice, on the accountability of donors and its impact, maybe unintended, on global institutions and processes.

"The rapid demise of public sector policy-making in key areas of public health, and the reliance on the Gates family and its staff, is impoverishing debate over public health priorities," says James Love, director, Knowledge Economy International (KEI), a US-based not-for-profit that seeks better outcomes to the management of knowledge resources. It is borne out by occasional outbursts from people within the system.

**Concentration of Power**

Some time ago, the head of WHO's malaria research revealed that the increasing dominance of the Gates Foundation was stifling diversity of views among scientists and that it could seriously impede the policy-making function of the world body. He was dismayed by the foundation's decision-making process: "A closed, internal process.accountable to none other than itself".

More recently, in January 2011, the Peoples Health Movement, a grassroots campaign for health for all, wrote to members of the WHO's executive board, calling attention to a number of issues. This included innovation, intellectual property rights (IPR), millennium development goals, and also the future of financing WHO, especially the unhealthy trend of donor money increasing in proportion to that of contributions from member states.

WHO's recent over-reliance on medicines, diagnostics and other technological fixes is being criticised. "Allocations to the social determinants of health have shrunk greatly," says Mira Shiva. "Water, food, sanitation and other social circumstances have a greater play on the health of the poor." Shiva has been an ardent proponent for the rational use of medicines.

In contrast, a humungous push on vaccines is underway. The Gates Foundation, for example, has allocated $10 billion to this field and describes this as the decade of vaccines. However, the GAVI Alliance, and some of the mechanisms it has fostered, is now under fire.

One such mechanism is the Advance Market Commitments (AMC), inspired and supported by the Gates Foundation. The AMC seeks to provide pharma companies a captive market for 10 years, provided they agree to develop and supply vaccines to developing countries, in millions of doses, at a deep discount. The pilot AMC of $1.5 billion, funded by the Gates Foundation and G7 countries, for pneumococcal diseases, which kills almost a million children annually, pays $3.50 per dose to the companies in the
mechanism (GlaxoSmithKline and Pfizer-Wyeth, among others). Recipient countries make a small co-payment. However, instead of developing new vaccines, the AMC brought in vaccines already developed by big pharma, for which costs had been recovered substantially from sales in western markets.

Donald W Light, a distinguished academic and visiting professor at Stanford University, was part of the AMC process, but found himself out of it when his views crossed that of big pharma. Light often dubs it the "advance procurement commitment" for its overwhelming bias towards big pharma and profits. "GAVI is basically setting the markets for big pharma," says Leena Menghaney, campaign co-ordinator (India), Medecins Sans Frontieres (MSF), a medical humanitarian organisation that won the Nobel Peace Prize in 1999.

The GAVI Alliance is already in a deep funding crisis. It is expected to scour for $4.1 billion this year, primarily because of action skewed in favour of big pharma. "Leaders of donor nations and GAVI board members should sit with the chairman of Pfizer and GSK to negotiate a new price near $2," says Light. "In the longer run, they should negotiate licensing, technology transfer and other ways to foster price-competition from other low-cost producers."

The suggestion is indeed relevant for the AMC, which disregards the immense potential of small pharma companies in developing countries to bring cheaper vaccines to the world. The Pune-based Serum Institute of India participates in the AMC, but when it requested funding support during its R&D process for a vaccine, it was turned down. Light is in favour of companies in the Serum Institute mould.

**Institutional Influence**

The Gates influence and stranglehold on global institutions and mechanisms in healthcare are quite evident. It doesn't stop here. Numerous proposals for a 'Medical R&D Treaty' as a more egalitarian alternative to the existing one, which links R&D costs to product prices, has been systematically snuffed out.

The treaty seeks to place global, and country-specific obligations, on funding medical R&D. Each country is expected to extend support on the basis of its national income. "It's regrettable that the Gates Foundation opposes discussions at the WHO on a possible treaty on medical R&D," says James Love. "An initiative that can create new global sustainability standards, promote access to knowledge, and usher much-needed transparency and ethical norms." At a press conference in New Delhi on Wednesday, Gates said: "I don't know about this treaty. I don't have a position on this."

Interestingly, while large organisations such as the WHO bear a tendency to capitulate easily to pressure, smaller, newer outfits show more spunk. The Drugs for Neglected Diseases Initiative (DNDi), a product development partnership, which also seeks funds from the Gates Foundation, has clear firewalls in place.

"We limit funds from a single donor to not more than 25% of our total requirement," says Bernard Pecoul, executive director, DNDi, which is seeking to raise euro 274 million by 2014. The Gates Foundation has committed around $40 million to DNDi. It demanded a board position, but DNDi refused.

But such instances of refusing to bow to big philanthropy are rare. "It's a crisis of accountability today," says Shiva. "It's no more accountability of corporations or philanthropists alone; the government too has a lot to answer".

**Reports say Ugandan anti-gay bill has been killed**

by Jessica Geen

25 March 2011, 4:33pm

Reports from Uganda say the country's anti-homosexuality bill has been dropped.

The controversial legislation would have strengthened Uganda’s current laws against gay sex but several reports say the government has intervened to drop it.

Information minister Kabakumba Masiko told Uganda’s NTV that another bill would cover much of the provisions in the anti-homosexuality bill.

He said: “We had the Cabinet Subcommittee which gave us a report yesterday and we did realise that there are many things that are in the bill that are covered by other laws that are already in place. ... And the law that is in offing, the Sexual Offenses Bill, will cover most of the other issues that were going to be covered.”

It is not yet clear what provisions are in the Sexual Offenses Bill.

It has been suggested that directives to drop the bill came from the office of President Yoweri Museveni.
Last January, Mr Museveni appeared to show concern over how the bill would affect Uganda’s global relations.

It “must take into account our foreign policy interests”, he said.

The bill was to be debated by the Law and Parliamentary Affairs committee.

Blogger Warren Throckmorton reported that MP David Bahati, the sponsor of the bill, said he had been assured by the Legal and Parliamentary Affairs committee chair Stephen Tashobya that debate would go ahead.

Manila interfaith rally draws 40,000 faithful vs. RH bill

Friday’s Interfaith Prayer Rally against the Reproductive Health (RH) bill drew as many as 40,000 of the faithful to the Rizal Park in Manila, according to officials of the Manila Police District.

The rally started at 4 p.m. and coincided with the Roman Catholic Feast of the Annunciation or Day of the Unborn. People in Metro Manila and from neighboring provinces flocked to the Quirino Grandstand to listen to speeches delivered by Manila Archbishop Gaudencio Cardinal Rosales and other prominent anti-RH bill personalities. (See: Pacquiao: If my dad used a condom, I wouldn’t be here now)

The Roman Catholic Church is against the RH bill, which allows for artificial means of contraception. The Church favors only natural family planning.

Friday night’s mass was one of several activities lined up by the Catholic Church to oppose the RH bill.

But one of the highlights of the program was an interfaith prayer against the RH bill led by religious leaders from the Catholic Church and even other faiths like Islam, Hinduism and Buddhism.

A number of prominent politicians also spoke at the gathering, some of whom were even political foes like Manila mayor Alfredo Lim and his predecessor Lito Atienza. Those who were not able to make it to the rally, like Senate President Juan Ponce Enrile and Sarangani Rep. Manny Pacquiao, just had their prepared speeches read to those at the gathering.

Church-run Radio Veritas reported some of the participants at the rally began to disperse at about 7 p.m., shortly before the mass started.

However, the radio’s anchors claimed this may be because some people in the crowd could not hear the announcements from the stage due to the inadequate sound system at the venue.

The rally ended with a candle-lighting ceremony.

Prelate: Avoid ‘moral tragedy’

At a mass highlighting the rally, Rosales said in his homily: “May panahon pa upang maiwasan ang trahedyang moral na idudulot ng RH Bill. May panahon pa. (There’s still time to avoid the moral tragedy that the RH Bill will bring us. There’s still time),”

The archbishop implored lawmakers to overhaul the RH Bill or junk it altogether, stating that it promotes disrespect for life and teaches the opposite of discipline and responsibility.

The prelate scored some lawmakers for promoting the bill, which he said encourages people to have irresponsible sex and to avoid the consequences.

“Sa ngalan daw ng sanidad at kalusugan, puro palusot ang gusto ituro sa kabataan ng ilang mambabatas. Ganyan ang magiging bukas ng Pilipinas. Mga mamamayang puro palusot, lahat na padulas ang alam,” he said.

(Some lawmakers would have children taught to shirk responsibility, in the name of health. This is what would become of the future of the Philippines, a citizenry that knows nothing but to make excuses.)

RH Bill against Pinoy culture?

Rosales said life should be respected, whatever stage it be in – as a fetus, an infant, an adult or an old person – adding that the Church believes life must be defended, and not be blocked by any artificial means.

“Ang paglapastangan sa buhay na yan, malakas man o mahina, na ating laging pinahalagahan ay labag sa kulturang Pilipino tungkol sa buhay ng tao (Disrespecting life – strong or weak – but which all of us hold dear, is against Filipino culture respecting human life),” he said.

Rosales said that all that is needed is for the married couple to practice discipline and hold back from having sex if the woman is fertile and the couple does not want to have a child yet.

“Kapag may disiplina ang tao may disiplina sa kama. Pag may disiplina sa kama may disiplina sa kalsada. Pag may disiplina sa kalsada may disiplina sa pitaka at kwarta ,” he said.
(If a couple exercises discipline, that discipline shows on the marital bed. If people are disciplined on the marital bed, they will be disciplined out in the streets. And when there’s discipline in the streets, there’s also discipline in handling money.)

The Manila archbishop lamented that some proponents of the RH bill are encouraging undisciplined sex and promoting artificial contraception as so-called protection from sexually transmitted diseases.

Stressing that marriage is holy and sex is sacred as a means of procreation, Rosales asked why children should be taught to use condoms to avoid disease when they are supposed to be taught to value life and exercise self-restraint and discipline.

**Gomburza vs. Damaso**

Rosales also threw jabs at individual supporters of the RH bill, including celebrated tour guide Carlos Celdran who had disrupted a Mass last year at the Manila Cathedral by raising a placard with the name “Damaso” while dressed up as national hero Dr. Jose Rizal.

Celdran, an advocate of the RH bill, branded bishops opposing the bill as “Damaso,” a reference to a fictional Spanish priest with dubious morals and motives, and who fathered a girl in Rizal’s novel *Noli Me Tangere*.

Rosales reminded the faithful that although Rizal wrote much anti-clerical rhetoric, he dedicated his novel *El Filibusterismo* to martyred patriotic priests Jose Burgos, Mariano Gomez and Jacinto Zamora.

Aside from Rosales, a senior official of the Vatican also delivered a message of encouragement to those who attended the prayer rally, telling them to love and protect life.

**Vatican and El-Shaddai**

At the start of the mass celebrated at the Quirino Grandstand, Manila Auxiliary Bishop Broderick Pabillo delivered the message of Vatican Secretary of State Tarcisio Cardinal Bertone.

Bertone recalled a message from Pope Benedict XVI to Manila-based Catholic bishops who had met with the pope at the Vatican last year: “I commend the Church in the Philippines for seeking to play its part in support of human life from conception until natural death, and in defense in the integrity of marriage and the family,” Benedict XVI had said.

“In these areas you are promoting truths about the human person and our society which arise not only from divine revelation but also from the natural law and order which is acceptable to human reason and thus provide a basis for dialogue and deeper discernment on the part of all people of goodwill,” Bertone quoted the pope as saying.

After the mass, El Shaddai leader Mariano Velarde led participants in reciting a prayer for life, and thanked the bishops for defending life.

He claimed that the RH bill was a “blasphemy” because it aims to “control the population growth of Filipinos,” which he said is opposed to God’s intentions.

**Davide to lead another anti-RH protest**

Meanwhile, former Chief Justice Hilario Davide Jr. will lead yet another protest against the anti-reproductive health (RH) bill in Manila this Sunday.

The Catholic Bishops’ Conference of the Philippines said it expects “thousands” to join the “walk for life” led by Davide along Roxas Boulevard in Manila.

"Organized by the Knights of Columbus (K of C) Philippines, a group of Catholic men, the march will kick off with a 6 a.m. Mass at the San Agustin Church in Intramuros,” the CBCP said.

The protest march is scheduled to start right after the mass, from Intramuros to Rajah Sulayman Park in Malate, where a program will be held.

Demonstrators will come from various Knights of Columbus Councils from the Dioceses of Antipolo, Cubao, Imus, Caloocan, Malolos, Parañaque, and Pasig, as well as the Archdiocese of Manila. The Knights of Columbus claim to have 150,000 members nationwide.

Aside from Davide, spearheading the march are Manila Mayor Alfredo Lim, and Knights of Columbus officials led by Luzon Deputy Alonso Tan.

Guest speakers include pro-life advocate Ligaya Acosta, executive director of Human Life International Asia.

Davide and Lim are also to deliver their messages during the program in Malate. – *With reports from Raffy Tima/MRT/JV, GMA News*
Sexually liberated, or just badly brought up?

Elena Fanailova, 23 February 2011

There was “no sex in the USSR” (that, at least, is what one Soviet woman famously declared in a 1986 TV talk show). Attitudes to sex in contemporary Russia have undeniably moved on from such social conservatism. But have they changed enough to be called a revolution, asks Elena Fanailova?

About the author: Elena Fanailova is an award-winning poet living in Moscow

A couple of years ago I was part of a group of young female writers on an Oxford University course called “Open World”. It took place in the American South, in a town immortalised by William Faulkner as Yoknapatawpha. One occasion we got into a discussion with the professor of Russian Literature about the strength of civic movements in the 60s in America and in Russia. The professor has a Russian wife and spent several years in Russia. He assured us that the dissident movement, and indeed all protest movements, in Russia had been weak and they played no part in influencing public mood. But, we cried, what about Oksudzhava, Natalia Gorbanevskaya and Vadim Delone? The Taganka Theatre, Vysotsky, Novocherkassk? The professor replied that we hadn’t had countrywide mass protest movements like the anti-segregation and anti-Vietnam movements in America. To prove his point he took us to the Memphis hotel on whose balcony Martin Luther King was shot, which has been turned into a Civil Rights Museum.

What we found most impressive was not so much the rooms where King and his friends had spent his last day, but the huge amount of film footage, which showed vast crowds of people. We watched old film showing whites and blacks in the South going pointedly into a restaurant that was “only for whites”, where they had boiling water poured over them. We saw them in the white districts forming a human chain and facing up to the Ku Klux Klan. In the North there were rallies with many thousands of people and a police presence. This crowd of demonstrators against segregation marching in a solid block from Capitol Hill made an indelible impression on me. In the Soviet Union rallies like this would only have been possible on 1 May or 7 November. To judge by the chronicle of the 1968 events in Paris, the marches of the elderly in support of de Gaulle were truly massive. The Soviet Union had never seen such quantities of people out in the streets until the Baltic uprisings or Tbilisi. Then there was August 1991 and Soviet people came out on to the street and would continue to do so until the beginning of the 00s.

In asking the question as to whether there has been a sexual revolution in Russia, one needs to look separately at information, society, medicine, psychology and sociology.

Lena Fanailova

A real revolution, not just a palace coup, is carried out in the name of the downtrodden masses. If one maps the mass participation in Western public movements into the area of sexual freedom, you get the idea that most people were liberated by the sexual revolution, which started after the Second World War in Europe and America and reached its peak in the 60s. Views on love, sex and the formation of family units will not be very different in British 60-year olds and 16-year olds of either sex. They are more likely to disagree on politics. Contraception and family planning, the political and social, but also emotional and sexual, equality of the sexes, feminism, common law marriages, the legitimisation of homosexuality and same sex marriages is one side of sexual liberation. The development of the porn and sex industries, including in their most perverted forms, is the other. For third-world countries the sexual revolution sometimes leads to the murder of feminist activists, and the sex-economy trade with Western sex-tourists.

Where is Russia with its claims to be great power on the map of the world sexual revolution? In asking the question as to whether there has been a sexual revolution in Russia, one needs to look separately at information, society, medicine, psychology and sociology

The information revolution

The information revolution was — by any account — substantial. “Little Vera” and “Interdevchka” [“international girl” – a Soviet-era prostitute who catered for clients with hard currency — ed] removed once and for all any ideas our fellow citizens might have had about taboos in the cinema. At the same time — and most importantly—taboos were being destroyed in video outlets and at home when we all watched (now it’s even a bit scary to remember the juxtapositions) “Emmanuelle”, “The Fruit is Ripe” and “Nine and Half Weeks” alongside Rambo and horror films. The intelligentsia was interested in “The Night Porter” and Pasolini and it was considered bon ton to receive one’s guests with the soundtrack of Roman Viktyuk’s “The Maids” on in the background. “Lolita” became available at the beginning of the 90s, and editions of Freud and the Kama Sutra started appearing.
One of the most popular perestroika films, Interdevochka, told the story of a hard currency prostitute of the 1980’s. To the Russian audience, the ‘Interdevochka life style’ was as fascinating as condemnable, and her material achievements were envious.

Journalists published (and not in samizdat) the manifestoes of revolutionary leaders dealing with the sex life of the proletariat. It transpired that after the 1917 revolution, there was an attempt at a sexual revolution in Russia and simultaneously moves to regulate it. The tabloid press was born from the wave of press freedom and was an essential sign of that freedom. It made it its business to find out about the personal lives of film stars and music hall stars, who in their turn started appearing nude on the covers of foreign magazines and Russian weeklies. One of the outstanding photographs of the 90s shows the actress Elena Koreneva on the cover of AIDS-INFO: the star of Andrei Konchalovsky’s films is no spring chicken, but she is photographed nude and unembarrassed with an antique glass of wine in her hand: vintage wine is, after all, better than young wine.

Like the words to their songs, the pop stars’ outfits are ever more explicit: the best of the home (or, more accurately, Ukrainian) pop projects is “ViaGra” which makes no bones about appealing to male erotic fantasies. On stage Boris Moiseev and his group are the embodiment of the liberated gay artist. Homosexuality is no longer a criminal offence and since 2000 the Russian sexual minority has been battling (so far unsuccessfully) for the right to hold gay marches in Moscow, a subject much discussed in the media. Beauty contests and lists of Russia’s sex symbols are now to be found regularly in the glossy and the tabloid press.

One can also talk about a revolution in the medico-social sphere, though there are local variances which leads to talk of social stratification and varying interpretations of sexual morals and behaviour in these countries. Contraception is available, though not everyone understands the need for it: less-educated men prefer to leave that question to the woman, or – more accurately – consider that it’s not their problem; the pill remains fairly expensive for those on low incomes.

Lena Fanailova

The naïve erotic shows at gangsters’ evening parties in the 90s, irony about Soviet sex in modern performance art of the same time and academic (i.e. ironic) exhibitions of Soviet underwear in the 00s, the destruction of erotic and religious taboos in the world of contemporary art...these were all signs of the times. How strange it is, by the way, that it’s only the religious element that attracts the attention of the Russian Orthodox Church, which brought a case against the exhibitions “Beware, religion!” and “Forbidden Art”.

In general, cinema without an erotic element has become a nonsense, just as in Soviet times cinema with hints of erotica. Russians can hardly forget scenes from “The Diamond Arm”, where Svetlana Svetlichnaya covers her breasts in front of the outraged heroine Nonna Mordyukova, or Svetlana Toma stripped to the waist in Emil Lotman’s romantic film “The Queen of the Gypsies”?

There is still, of course, a stigma attached to discussions in the open media about paedophilia (I remember only one analytical work in the journal “On Guard” in 1999) and BDSM (in spite of the fact that it is widespread in big cities, including among middle managers). These subjects provoke public aggression and are on the whole only discussed in Western press and in a penal context.

Society and medicine

One can also talk about a revolution in the medico-social sphere, though there are local variances which leads to talk of social stratification and varying interpretations of sexual morals and behaviour in these countries. Contraception is available, though not everyone understands the need for it: less-educated men prefer to leave that question to the woman, or – more accurately – consider that it’s not their problem; the pill remains fairly expensive for those on low incomes. At this level women prefer to leave decisions to the men in everyday life and in sexual matters too, as they did in Soviet times, ignoring the implications for their health, according to specialists.

After a public discussion and chiefly as a result of local initiatives, schools are beginning to provide sex education lessons. The Orthodox Church has come out against sex education lessons in secondary school and Patriarch Kirill has initiated a move to put a stop to them. Whether this succeeds or not is a question of ideology, as indeed is the influence of the Church on the way people behave, which includes sexual mores. The fact that there is a choice of gynaecologist or urologist, that both treatment and early abortions can be anonymous has put an end to the humiliations of Soviet times, but this is a privilege accorded only to the educated and well-off.

I still remember something that happened 20 years ago and wonder if it would be possible today: a girl friend of mine, a final year medical student, decided to lose her virginity surgically. She did this because, after two attempts, she realised that she would not be able to have a full sex life without this help.
She was refused the operation on the grounds that she was trying to have sex outside marriage. Her third partner managed to solve her problem, as she said, but this resulted in frigidity and considerable problems with sex thereafter.

*Russia has no real programme for sex education. Feminist activists want to change that*

An endocrinologist from a local district polyclinic told me some years ago she was sure that hormonal disorders in women over 30, including thyroid problems, were linked to the sexual revolution of the 90s (her words), just as much as to the deterioration of the ecological environment. What she meant was divorce for social reasons and frequent changes of sexual partners, which for Russian (Soviet) women with their parental steer towards patriarchal marriage represented psychological trauma. I don't know if she suggested her patients should live by the patriarchal moral code, or that they should see a psychotherapist — I never went back to her after that one visit.

It would be interesting to see the statistics for sexually transmitted diseases for those years at various social levels: on the one hand people are more educated and want to live a bourgeois life, but on the other increasing dumbing down leaves little room for hope.

**The social space: getting to know people and making friends**

In the 80s, even the 90s, to be a single girl in a café (or, heaven forfend, a restaurant!) was considered risky. The exception to this was the Baltic States: there groups of girls, or even a girl on her own, did not invariably become an object for male attention. On the whole people got to know each other in school, at the institute, at work or at specially arranged evenings; boys went to meet girls at friendly student hostels, which is where sexual contact took place, but vigilante raids were not uncommon and they led to dressings down at Komsomol meetings, though not for one offence — a pair or one of a pair had to have broken the rules frequently. Places of refuge for amorous couples were parental flats when they were away or, when it was warm enough, wooded parks or entrance halls to apartment blocks. Sex in a cemetery was considered pretty exotic, but that is more of a myth. Restaurants were regarded as places of depravity and pick-ups, where girls went for one reason only. In 1992 one of my young girl friends and her friend were beaten up in a bar by a bouncer because they had said they didn’t want to spend any more time with him. They told their story to journalists, who published critical articles along the lines of what kind of normal girl would go to a bar without a man?

In the 00s the mood changed in big cities with the opening of sufficiently democratic restaurants and bars catering for any social or erotic taste: in "Propaganda" you could dance, or you could find a partner for the night; in "Project O.G.I" or "Mayak" you could drink vodka, talk all night and part friends for life. Or you could go home alone from any of these venues, proud and happy, for this is also a form of sexual behaviour and freedom. In "Vogue Café" or in the establishment at Kazan Station a blonde could meet her destiny in the form of an oriental mini-oligarch or an exotic trader who had just arrived (despite the best efforts of the Moscow authorities to spread hatred to "immigrants" or "people not from here"). Moscow has become an international Babylon and the sexual footprint is ever more international, though xenophobes of every stripe and colour make huge efforts to prevent it.

The clubs, the parties, the expats...the only disturbing thing is that they are only interested in girls younger than 36 and men younger than 60. This has a whiff of ageism, though the educational work carried out by our pop stars has shown that unequal marriages don't have to be like the Pukirev picture: they are quite possible without the mercenary factor, where there's real love and harmony. Well-off Russians can get a feel for this when they go to foreign holiday destinations: couples where the woman is about 10 years older than the man are plentiful, one in three, and the women don’t even try to hide their age. These are the results of the Western sexual revolution.

The first naïve striptease joints of the 90s and the 00s are now rather more lacquered. There are striptease clubs for men, but also for women (no age limits, mainly in Moscow) and homosexual clubs (thought at the time of writing this article one of them had just been closed down by the city authorities, apparently after complaints from the neighbours). At the same time, the glossy magazines publish the revelations of the "ladies from Rublevo" [expensive Moscow suburb ed] and their visits to the “Little Red Riding Hood” striptease club. These ladies acknowledge that they independent of their husbands, both economically and emotionally, and that they are trying to find distraction and an emotional breathing space for money.

The information I have about prostitution and its distribution in establishments and public spaces is sketchy. Two years ago I observed a couple of places in the subway near Dinamo metro station and in Staropimenovsky lane, which is where the film “The Spot” was shot, partly using professional prostitutes. My friends in the know say that the number of high class prostitutes in Moscow is at an all time low. It’s no longer a prestigious profession: at the beginning of the 90s it was educated girls whose dream was to
catch a rich client and marry him, now the girls are provincial and from the working class suburbs of Moscow. But male prostitution is now very like female prostitution was at the beginning of the 90s, according to my well informed friends.

**Relationships formal and informal**

This brings us to the psychology and the anthropology of sexual relations. It's true that society has become more tolerant of common law marriage and relationships outside marriage: a man's career is not ruined if he has a mistress, neighbours don't any longer give divorced or single women funny looks, a single man in a big city is not likely to be described as gay and some people know the word “metrosexual” (though young homosexuals are drawn to the big cities, as there's more freedom of all kinds, including sexual, there). A young couple (including homosexuals) encounter no obstacles to renting a flat, as long as they have the money. Young people in jeans with tears on their bottom no longer attract critical looks, except in the provinces (though in the big cities many people find it off-putting deep down, however liberal they may be). People enter lightly into sexual relationships and part more easily.

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*Lena Fanailova*

At the same time patriarchal society, which has been catapulted into savage capitalism, legitimises biological and social instincts. For instance a rich elderly man and pretty young woman (or man – same sex couples are regarded as legitimate in the artistic world). Social and personal prejudices do not permit open discussion of sexual problems, be they physical or psychological. The woman is still servant to the man and the young are servant to the old, but I am not inclined to blame the men or the old, as it's a centuries-old social contract which suits both sides. The man (the older in a homosexual couple) earns the money and takes on the social responsibility, the woman (or younger man) evidently accepts the situation, expects presents in return for sexual favours and has none of the feelings of anxiety connected with free choice. The women complain of the men's indifference and the men complain of the women’s materialism. Under the new capitalism relationships have become businesslike, superficial and interested in erotic and economic advantage. This last existed in Soviet times too, but it was not done to talk about it.

Homosexuals and single people have approximately the same problems. As well as the points already listed, homosexuals have no model for their relationship or social tradition of the experience of life as a couple, so they either act out a traditional patriarchal relationship or base their union on a professional, business partnership. In leaving behind one kind of un-freedom they are forced to look for another. Everyone suffers if there is no love, not very good sex, loneliness or a desperate need for personal space within a marriage. 40-year olds get confused when love and sex change places. 60-year olds have grown up with the patriarchal model. There are new conservatives among the 20-year olds: a successful marriage in all respects, including economically and socially, is considered an absolute, which is more important than sexual, social or personal freedom.

In conclusion, Russia has too many geographical and economic zones with different ways of life to enable us to conclude that the sexual or social revolution can be accomplished in 25 years. Indeed, as we used to sing in one of the Soviet songs, “the revolution has a beginning, but it has no end”. At the same time, the friends I interviewed for this article were overwhelmingly of one viewpoint. Regardless of age, family circumstances, sexual orientation and social standing, only one disputed the assertion that Russia had experienced a sexual revolution in Russia in the years since 1991.

**Two-Thirds of South African Women at Risk for Cervical Cancer**

*The Times (Johannesburg),* (03.14.2011) South African Press Association

The head of the National Health Laboratory Service and of anatomical pathology at Witwatersrand University is warning of a rise in human papillomavirus (HPV)-related diseases among South African women.

Martin Hale said data from the World Health Organization (WHO) show increasing incidence of cervical cancer and other cancers associated with the STD.

“Information from a recent WHO/[Institut Català d’Oncologia] report on HPV and cervical cancer shows that South Africa has a population of 16.84 million women ages 15 years and older who are at risk
of developing cervical cancer,” said Hale. Using July 2010 estimates from Statistics South Africa, this amounts to roughly 65 percent of women in the country.

“Cervical cancer is the second-most frequent cancer among women in South Africa, and the second-most frequent cancer among women between 15 and 44 years of age,” said Hale. “Current estimates indicate that every year 5,743 women are diagnosed with cervical cancer and more than 3,000 die from the disease.”

Limited access to cervical cancer information and resources, as well as the HIV pandemic, are contributing to the increase. Hale said females are more susceptible depending on their age at first intercourse, the number of children they have had, and whether their immune system has been weakened.

“Public education, a regular Pap smear and modifying human behavior will assist in mitigating the rise in cervical cancer cases,” said Hale. Vaccines against HPV “have the potential to reduce the incidence of cervical and other anogenital cancers ... however the debate is still raging on how, to whom and whether the [immunizations] should be administered,” he noted.

### Integrated Behavioral Intervention to Improve HIV/AIDS Treatment Adherence and Reduce HIV Transmission

*American Journal of Public Health Vol. 101; No. 3: P. 531-538*, (03.01.2011) Seth C. Kalichman, PhD; Chauncey Cherry, MPH; Moira O. Kalichman, MSW; Christina M. Amaral, BA; Denise White, MA; Howard Pope, BA; Connie Swetzes, LPN; Lisa Eaton, PhD; Rene Macy, MA; Demetria Cain, MPH

The current study concerns an integrated behavioral intervention designed to enhance the use of HIV treatment as prevention by improving medication adherence, reducing risks for other STDs, and minimizing risk compensation beliefs. The authors conducted a randomized clinical trial to evaluate the intervention.

A total of 436 persons with HIV/AIDS participated in the trial, which compared the intensive behavioral intervention with an attention control condition. The researchers used unannounced pill counts to monitor adherence to antiretroviral (ARV) therapy. Computerized interviews were used to assess risk behaviors.

The findings indicated that the intervention demonstrated increased ARV adherence and less unprotected sex with nonseroconcordant partners at three- and six-month follow-ups, and fewer new STDs diagnosed over the nine-month follow-up period (adjusted odds ratio=3.0; P<.05; 95 percent confidence interval=1.01, 9.04). In addition, the intervention decreased behavioral risk compensation beliefs.

“A theory-based integrated behavioral intervention can improve HIV treatment adherence and reduce HIV transmission risks,” the authors concluded. “HIV treatment as prevention should be bundled with behavioral interventions to maximize effectiveness.”

### Research proves no 2 of us are alike, even identical twins

**Study tries to pinpoint the genetic determinants of schizophrenia**

Just like snowflakes, no two people are alike, even if they're identical twins according to new genetic research from The University of Western Ontario. Molecular geneticist Shiva Singh has been working with psychiatrist Dr. Richard O'Reilly to determine the genetic sequencing of schizophrenia using identical or monozygotic twins. The study is published in this month's PLoS ONE.

Singh looked at about one million markers of identical twins (and their two parents) where only one twin had schizophrenia. "The most informative feature of schizophrenia is that it sometimes runs in the family. So, for example, the risk of developing schizophrenia is much higher if your brother, sister, mother or father have the disease," says Singh, noting in the general population about one percent have schizophrenia. "We started with the belief that monozygotic twins are genetically identical, so if one member of identical twins has schizophrenia, then the risk for the other twin should be 100 percent, if it's all due to genes. However, studies over the years have shown that the risk of the disease in both twins is only 50 percent." That means either the twins are genetically not identical or the familial disease involves non-genetic (random) effects.

Singh and his team have now demonstrated that the monozygotic twins are not genetically identical. "So if schizophrenia is in the genes, then the difference in the genetic makeup of monozygotic twins, with only one disease twin, must have something to do with the disease." Singh found about 12 per cent of DNA can vary across individuals, "Cells are dividing as we develop and differentiate. More importantly, these cells may lose or acquire additional DNA. The genome is not static."
Dr. O’Reilly hopes this research will lead to better understanding and improved treatments for schizophrenia. “If we had a genetic test for schizophrenia, it could be applied early in the disease when it’s hard to make that diagnosis,” says Dr. O’Reilly.

‘Near perfect’ adherence in early stages of Partners PrEP study
Gus Cairns
Published: 29 March 2011

Very high levels of adherence have been achieved in one of the ongoing randomised controlled trials of oral pre-exposure prophylaxis (PrEP), according to a poster presentation at last month’s Conference on Retroviruses (CROI).

According to investigators in the Partners PrEP study, adherence levels of 99% were achieved by participants during an average four-month period during the two-year study.

Partners PrEP is a study amongst 4700 heterosexual couples of differing (serodiscordant) HIV status at nine sites in Kenya and Uganda. The HIV-negative member of each couple will be randomised into three groups to take a daily pill containing tenofovir, or tenofovir plus FTC, or a placebo. All pills will look identical. At the end of the study HIV incidence rates in the three trial arms will be compared. Results are expected by early 2013.

Achieving high adherence to the study medication in trials of new biomedical prevention methods such as microbicides and oral PrEP has been a challenge in studies so far, even those achieving a successful result.

Conventional methods of adherence monitoring such as self-report have proved to be unreliable, as drug level monitoring (in the iPrEx PrEP trial) and the use of microbicide applicators sensitive to vaginal mucus (in the Carraguard microbicide trial) have shown that participants’ actual use of trial interventions is considerably lower than their reported use.

This not only compromises the potential efficacy of the intervention, it makes it very difficult to interpret trial data, as ‘intent-to-treat’ efficacy (based on which arm participants were allocated to) will be very different from ‘as-treated’ efficacy (based on whether they actually used the treatment or not), and this does not help to answer the question of what adherence and efficacy would be in ‘real world’ situations.

To try to get round this, investigators from the University of Washington, Seattle, who are coordinating the Partners PrEP study, used three different ways of measuring adherence:

- Clinic-based pill counts, based on subtracting the number of pills actually prescribed from the number that would have been if every pill had been taken:
- MEMS (Medical Event Monitoring System) caps, an electronic device which sends a radio signal to clinic monitors when a pill bottle is opened
- Unannounced pill counts, in which trial assistants visited participants at random times once every month and counted the number of pills they had at home. There were an average 3.3 visits per trial participant.

None of the adherence measures excluded the possibility that participants are simply throwing their pills away rather than taking them, but the MEMS and home pill count measures at least means they are not being left in unopened bottles.

One in seven trial participants were recruited at an ancillary adherence study of whom 544 (11.6%) of participants contributed adherence data to this study. Thirty-six per cent entered the adherence study at the time they started the main study while others entered it at varied times during the study. Their adherence so far has been followed for a median of four months.

During this time, adherence as measured by all three measures exceeded 99%—it was 99.6% by clinic count, 99.1% by unannounced pill count, and 101.9% by MEMS. This ‘over 100%' figure means that either participants are taking more than the prescribed dose or that they are opening medicine bottles without taking doses at times.

Adherence below 80% was found in 35 participants (6.4%) by unannounced pill count. The only characteristic related to poor adherence was youth: poor adherence was 10% less likely for every ten years older in participants.

Adherence as measured by clinic count and self-report in the iPrEx trial was 93%, yet a substudy of drug levels showed that only 50% of participants were actually swallowing their pills. Although the present study cannot predict what participants’ adherence will actually turn out to be when Partners PrEP...
reports, its additional two measures and very high reported levels so far suggest adherence may turn out to be better than in iPrEx.

**Reference**

**Watch for malnutrition risk in children with HIV after starting ART**

Carole Leach-Lemens  
Published: 29 March 2011

One in nine HIV-infected children with advanced illness was hospitalised with severe malnutrition within 12 weeks of starting antiretroviral and these children had a 15-fold increased risk of dying within the first six months compared to those children not hospitalised, Andrew Prendergast and colleagues reported in the ARROW study published in the advance online edition of AIDS.

The high frequency of new cases of severe malnutrition in children after starting antiretroviral therapy (ART) is not easy to explain say the researchers, and they warn that health care workers need to be alert for the condition, especially in children who are already malnourished.

Treatment programmes for children also need to integrate HIV and malnutrition care, and look at whether nutritional supplementation before starting treatment can protect against development of severe malnutrition once ART begins.

Antiretroviral Research for Watoto (ARROW) is an open-label, randomised trial of induction-maintenance and monitoring strategies for antiretroviral treatment in 1207 HIV-infected children with a median age of 6 (3-17) in three hospitals in Uganda and one in Zimbabwe recruited from March 2007 to November 2008.

HIV infection and malnutrition among children in resource-limited settings cannot be separated. HIV prevalence is high in children with severe malnutrition. The risks of dying are three times greater in HIV-infected children with severe malnutrition than in uninfected children with severe malnutrition.

In resource-poor settings HIV infected children are likely to be seriously ill and severely malnourished when they present for care. Studies show 5-10% early death in children starting ART in these settings

The two primary clinical manifestations of severe malnutrition are:
- non-oedematous (no swelling) malnutrition (marasmus) and
- oedematous (oedema or build up of swelling in the tissues or circulatory system) malnutrition (kwashiorkor and marasmic kwashiorkor).

The authors note that while marasmus is most often associated with HIV-infected children anecdotal reports suggest that oedematous malnutrition can occur in children soon after starting ART.

The authors wanted to better understand the effect of SM on early death in children soon after starting ART. They looked at the frequency of hospitalisations and change in CD4 percentages 12 weeks after the start of ART and death and change in Z score by six months.

Severe malnutrition (SM) in this study was defined as one or more of:
- Kwashiorkor: 60-80% of weight for age with oedema
- Marasmus: <60% of weight for age without oedema
- Marasmic kwashiorkor: <60% of weight for age with oedema.

Children were assessed for SM before enrolment. Children with SM before enrolment got 2-8 weeks of supplementary feeding.

At enrolment children began cotrimoxazole prophylaxis and started abacavir, lamivudine and either nevirapine or efavirenz. Children randomised to an induction-maintenance therapy also got zidovudine in the first 36 weeks. Children were followed up every four weeks for clinical evaluation, height and weight and CD4 count and percentage measurements.

After starting ART children were hospitalised for SM if they developed oedema, loss of appetite and/or concurrent infections needing treatment.

No child had oedema before starting ART.

3.2% (39) of children were hospitalised for SM, 20 with oedema (11 kwashiorkor and 9 marasmic kwashiorkor); 19 had marasmus.

The median time from starting ART to hospital admission for those with swelling (oedema) was 26 days (IQR: 14-56) and 28 days for those without (marasmus) was 28 days (IQR: 14-36).
74% (29) of children with SM admitted to hospital had underlying infections. Similar proportions were seen in children with oedematous malnutrition or with non-oedematous malnutrition. Children hospitalised for SM had significantly lower baseline weight-for-age, height-for-age, weight-for-height and mid-upper arm circumference than those not admitted.

Among the 220 (18%) children with advanced illness 7.3% (95% CI: 3.8-10.7) developed kwashiorkor and 3.6% (95% CI: 1.2-6.1) developed marasmus within three months.

The authors highlighted that over half of the children hospitalised for SM developed oedema after starting ART. While marasmus is more common in HIV-infected children their findings support anecdotal evidence from sub-Saharan Africa suggesting starting ART may play a role in this contrary finding.

They suggest that since many children in resource-poor settings will start ART at an advanced stage it is wise for treatment programmes to anticipate oedematous malnutrition.

While the reasons for the onset of kwashiorkor are unclear, the authors offer several suggestions, which may not be mutually exclusive:

1) The decline in immune activation and increase of CD4 cell count after starting ART may result in the development of oedema.
2) The onset of kwashiorkor shortly after starting ART may be yet another presentation of immune reconstitution inflammatory syndrome (IRIS).
3) Onset of oedema may be a manifestation of refeeding syndrome, a range of metabolic and physiological disturbances that can occur when food is introduced after a period of starvation. Refeeding syndrome might occur as a result of an increased appetite after starting antiretroviral therapy, itself a widespread phenomenon according to anecdotal reports.
4) It may be a form of ART toxicity specific to malnourished children. Severe manifestations of well-known toxicities are more common in HIV-infected people with very low nadir CD4 cell counts. In those with oedematous malnutrition the median CD4 count was 2.5, an extremely low level.

Death rates among children hospitalised with SM were high. At six months the death rates were 32%, 20% and 1.7% among children hospitalised with marasmus, kwashiorkor and not hospitalised, respectively (p<0.001).

“There is an urgent need to understand better the complex interplay between malnutrition, infection and immunodeficiency” the authors note.

The authors conclude “integration of HIV/malnutrition services and further research to determine optimal ART timing, role of supplementary feeding and antimicrobial prophylaxis are urgently required.”

Reference
Prendergast A et al. Hospitalisation for severe malnutrition amongst HIV-infected children starting antiretroviral therapy in the ARROW trial. AIDS, Advance online publication, March 2011 DOI: 10.197/QAD.0b013e328345e56b

Charge of infecting partner with HIV quashed
Published: 8:33AM Wednesday March 30, 2011 Source: Fairfax
A man accused of infecting his partner with the HIV virus got off the charge when police could not find the alleged victim to quiz her after doubts were raised about her honesty.

In the High Court at Wellington, a judge suppressed the name of the man who had denied wounding with intent to cause grievous bodily harm.

Police said he did not tell his partner he had HIV, the couple had unprotected sex and she contracted the disease.

The man said his partner of several years knew of his condition and that they always had protected sex.

Shortly before the trial was due, information came to light which, if true, would have affected a court’s view of her honesty. Police were unable to find her and thought she was hiding from them.

They had wanted to check the information before expensive tests to see if the couple had the same strain of HIV.

The Crown offered no evidence against the man, resulting in a discharge which amounted to an acquittal.

Jo Murdoch, a lawyer from the Public Defence Service, successfully argued in court that the man's identifying particulars should be suppressed.

Justice Simon France said the issue became whether the man’s HIV status—a particularly private and sensitive medical fact—should be exposed when grave doubts had been raised about the alleged victim’s credibility.
The case did not have the public interest element of a person accused of having put multiple partners at risk or having risky casual sex. Also, the alleged crime was irrelevant to his employment and his contact with the public generally.

Taken together the circumstances outweighed the usual principle that justice should be carried out publicly, Justice France said.

Could HIV-infected organs save lives?

Johns Hopkins researchers argue for reversing ban on transplanting infected organs and making them available to HIV-infected patients

If Congress reversed its ban on allowing people with HIV to be organ donors after their death, roughly 500 HIV-positive patients with kidney or liver failure each year could get transplants within months, rather than the years they currently wait on the list, new Johns Hopkins research suggests.

"If this legal ban were lifted, we could potentially provide organ transplants to every single HIV-infected transplant candidate on the waiting list," says Dorry L. Segev, M.D., Ph.D., an associate professor of surgery at the Johns Hopkins University School of Medicine and the study's senior author. "Instead of discarding the otherwise healthy organs of HIV-infected people when they die, those organs could be available for HIV-positive candidates."

Not only would HIV-positive transplant candidates get organs sooner if such transplants were legalized, Segev says, but by transplanting those patients and moving them off the waiting list, the time to transplant would be shorter for non-HIV-infected patients.

The ban on organ donation by HIV-positive patients is a relic of the 1980s, when it was still unclear what caused AIDS, at the time a devastating new epidemic sweeping the United States. Congress put the ban into the National Organ Transplant Act of 1984 and it has never been updated, despite the fact that HIV is no longer an immediate death sentence but a chronic disease managed with medication.

The number of HIV-positive patients receiving kidney or liver transplants — with non-HIV-infected organs — is on the rise as doctors become more comfortable with the idea, and patients are having good outcomes, Segev says. In 2009, more than 100 HIV-positive patients got new kidneys and 29 got new livers. HIV-infected patients may encounter accelerated rates of liver and kidney disease due in part to the toxic effects of antiretroviral therapy, the medications that keep HIV at bay.

Segev and his colleagues set out in their study, published early online in the American Journal of Transplantation, to estimate the number of people who die each year in the United States who are good potential organ donors except for that they are HIV-positive. They culled data from two main sources — the Nationwide Inpatient Study, which has information on in-hospital deaths of HIV-infected patients, and the HIV Research Network, a nationally representative registry of people with HIV. The team determined that the number of annual deaths with what are believed to be organs suitable for transplantation was approximately the same as estimated by each data source — an average of 534 each year between 2005 and 2008 in the Nationwide Inpatient Study and an average of 494 each year between 2000 and 2008 in the HIV Research Network.

While no transplants of HIV-infected organs into HIV-infected patients have been done in the United States because of the ban, Segev says doctors in South Africa have started doing this type of transplant with excellent results.

Segev suggests that, in transitioning to a system where HIV-infected donor organs can be transplanted into HIV-infected patients, doctors can call on the lessons and experience of transplanting hepatitis C patients with organs from people with the same disease. This practice, which has not always been the standard, has substantially shortened the waiting list for these recipients without significantly compromising patient or graft survival. The decision of whether or not to use these organs is not a legal one, but one made by the clinician.

Using HIV-infected organs is not without concerns. There are medical and safety issues that need to be addressed. Doctors need to make sure that the harvested organs are healthy enough for transplant and that there is minimal risk of infecting the recipient with a more aggressive strain of the virus. There is also a fear that an HIV-infected organ could accidentally be transplanted into an HIV-negative recipient. Segev says that hepatitis C-infected organs are clearly marked as such and similar protocols can be developed with HIV-infected organs.

"The same processes that are in place to protect people from getting an organ with hepatitis C accidentally could be put in place for HIV-infected organs," Segev says. "When you consider the
alternative — a high risk of dying on the waiting list — then these small challenges are overshadowed by the large potential benefit."

Segev says eliminating the prohibition on HIV-infected organ donation would have immediate results. At first, he predicts, there would be more HIV-infected organs than people on the waiting list. Then, as doctors realized that their HIV-infected patients would no longer have to wait five-to-seven years for a transplant, Segev says he thinks more and more HIV-infected patients would sign up for the shortened list for an HIV-infected organ.

"The whole equation for seeking a transplant for someone with HIV and kidney or liver failure would change if this source of organs became available," he says. "We want the decisions taken out of the hands of Congress and put into the hands of clinicians."

**Rwanda Investigating Adult Male Circumcision Without Anesthesia**
*Scientific American*, (03.16.2011) Clementine Wallace

Rwanda’s government is studying a new nonsurgical method to circumcise males as part of its fight against HIV. The experimental PrePex device, manufactured by Circ MedTech, includes an elastic mechanism that is clamped on the penis foreskin in about four minutes, without anesthesia or sutures. With its blood supply cut, the foreskin dries up and it is removed after a week, and no blood is lost.

In March 2011, data on the first 40 patients in a safety and efficacy trial were presented at the 18th Conference on Retroviruses and Opportunistic Infections in Boston. All the men healed excellently, said researchers.

Participants took two ibuprofens to cope with an initial three-hour period of discomfort, said Agnès Binagwaho, permanent secretary of Rwanda’s Ministry of Health. Newly circumcised males are counseled to forego sex for six weeks after the foreskin is removed.

“If we only circumcise newborns, the effects will start in 15 years,” Binagwaho explained of Rwanda’s aim of circumcising 2 million adult males by 2012. “We are offering, alongside counseling, testing and condom distribution, an additional means of lowering transmission. It’s a comprehensive approach.”

“There’s absolutely no doubt that if one can perform male circumcision without anesthesia, you save time, money and it requires less expertise,” said Kim Eva Dickson, senior advisor in WHO’s HIV/AIDS department. “We saw it done, and when we spoke to people who went through the procedure they seemed satisfied and the cosmetics looked good.”

A randomized controlled trial with 150 participants is ongoing; it will compare PrePex with conventional, surgical circumcision. Experts agree the device still has to be tested in expanded trials to ensure it is not associated with any rare adverse events.

For infants, World Health Organization-approved circumcision devices include the Morgen clamp, the Gomco clamp and the Plastibell.

**Public Campaign Ad Featuring Patient Draws Criticism**
*Korea Times (Seoul)*, (03.28.2011) Kim Tae-jong

A new hepatitis B virus awareness campaign’s TV advertisement is being criticized as too vivid and intense. Sponsored by the Korean Association for the Study of the Liver (KASL), depicts an HBV patient with jaundice and other signs of end-stage disease. The ad, which stresses the importance of regular medical checkups, is now being re-edited in response to the concerns.

“I felt like I’m dying soon. It’s terrifying. It just made me feel hopeless,” wrote one member of an online community for HBV patients. A number of similar comments were posted at patient-support websites, with some demanding the ad be pulled.

“The ad violates the human rights of the patients with the disease, which is overlooked in the name of disease prevention,” another website member posted.

Online criticism also said the ad may imply that carelessness led to the patient being infected with HBV. Some 3.5 million South Koreans, or 5 percent to 8 percent of the population, have chronic HBV, and discrimination is still very much a concern.

“Watching the ad, people will not want to hire a carrier of the virus or marry him or her,” said one site user. “Why did a censorship body allow such a horrible and discriminative ad to be aired?”

“In the beginning, we focused on showing the tragic outcome so that people would recognize the seriousness of the disease and the importance of regular medical checkups,” a KASL official said in response. “We hope people understand our original intentions.”

A new version of the ad will debut in April.
Association of Aging and Survival in a Large HIV-Infected Cohort on Antiretroviral Therapy

AIDS Vol. 25; No. 5: P. 701-705, (03.13.2011)  Celestin Bakanda; Josephine Birungi; Robert Mwesigwa; Nathan Ford; Curtis L. Cooper; Christopher Au-Yeung; Keith Chan; Jean B. Nachega; Evan Wood; Robert S. Hogg; Mark Dybul; Edward J. Mills

The authors undertook the prospective observational study to determine whether there is a “significant difference in survival between elderly (>50 years) and nonelderly adult patients receiving combination antiretroviral therapy [ART] in Uganda between 2004 and 2010.”

Patients enrolled in the AIDS Support Organization Uganda HIV/AIDS national program were evaluated for time to all-cause mortality. The investigators applied a Weibull multivariable regression.

Of the 22,087 patients in the analyses, 89.0 percent (19,657) were ages 18-49 and 11.0 percent (2,430) were age 50 or older. “These populations differed in terms of the distributions of sex, baseline CD4 cell count and death. The age group 40-44 displayed the lowest crude mortality rate (31.4 deaths per 1,000 person-years; 95 percent confidence interval 28.1, 34.7) and the age group 60-64 displayed the highest crude mortality rate (58.9 deaths per 1,000 person-years, 95 percent CI 42.2, 75.5),” the results showed. Nonelderly patients had better survival than elderly patients (P<0.001), per Kaplan-Meier survival estimates. Adjusted Weibull analysis indicated that elderly age status was significantly associated (adjusted hazard ratio 1.23, 95 percent CI 1.08-1.42) with mortality, after controlling for sex, baseline CD4 cell count and year of ART initiation.

“As antiretroviral treatment cohorts mature, the proportion of patients who are elderly will inevitably increase. Elderly patients may require focused clinical care that extends beyond HIV treatment,” the study authors concluded.

Volunteers Needed for HIV Trials

The Tennessean (Nashville), (03.20.2011)  Tom Wilemon

Vanderbilt University’s HIV Vaccine Trials Unit is encouraging high-risk, HIV-negative men ages 18-45 to enroll in a trial testing a new HIV vaccine strategy.

Nashville is one of 12 sites chosen by the National Institutes of Health for the HVTN 505 trial, which will test a prime-boost vaccine approach against HIV. Sponsored by the National Institute of Allergy and Infectious Diseases, the trial is being conducted by the NIAID-supported HIV Vaccine Trials Network.

Researchers aim to sign up at least 60 men for the Nashville arm of the study. Kyle Rybczyk, director of the Vanderbilt unit, wants to enroll even more than 60, as the study began accepting volunteers in 2009 and total national enrollment was only 883 as of mid-March of this year. To determine efficacy, the trial needs at least 1,350 volunteers.

Researchers are hoping to learn whether this particular vaccine regimen could decrease the viral load of people who become infected with HIV. Usually, the lower the viral load, the longer it can take to progress to AIDS, according to the network. A lower set point may delay illness and help lower transmission.

Participants will get a series of three immunizations with a recombinant DNA-based vaccine over eight weeks, followed by a single recombinant booster at week 24, or placebos. The DNA priming shots, as well as the adenovirus serotype 5 booster, contain more pieces of HIV DNA than the earlier STEP trial. In addition, the ad5 virus has been weakened more than the STEP trial version, expressing less adenovirus genes while still carrying HIV gene segments to the immune system, the network said.

Efficacy data should begin to develop two years into the study, said Dr. Spyros Kalams, a Vanderbilt immunologist. Those interested in volunteering can visit www.HopeTakesAction.org or telephone 615-322-HOPE.

Vaccine Used in STEP Trial Alters HIV Genes

SUMMARY: The adenovirus vaccine candidate used in the STEP trial did not significantly reduce HIV infection, but did alter the genetic makeup of the virus, according to a recent report in Nature Medicine.

Below is an edited excerpt from a press release issued by the University of Washington describing the research.

For First Time, Scientists Show an HIV Vaccine Impacts the Genetic Makeup of the Virus Results suggest new vaccine strategies to debilitate viruses by tapping into this response

125
March 1, 2011—An AIDS vaccine tested in people, but found to be ineffective, influenced the genetic makeup of the virus that slipped past. The findings suggest new ideas for developing HIV vaccines.

The results were published Feb. 27 in Nature Medicine.

This is the first evidence that vaccine-induced cellular immune responses against HIV-1 infection exert selective pressure on the virus. "Selective pressure" refers to environmental demands that favor certain genetic traits over others.

The senior author of the multi-institutional study is Dr. James I. Mullins, University of Washington (UW) professor of microbiology. The research team analyzed the genome sequences in HIV-1 isolated from 68 newly infected volunteers in the STEP HIV-1 vaccine trial. Mullins and the other principal researchers who carried out this study were not involved in the STEP trial.

The STEP trial was a double-blind, Phase 2B test-of-concept of a Merck HIV-1 subtype B vaccine. The vaccine, MRKAd5, was designed to make the body produce infection-fighting white blood cells, commonly called killer T-cells, that could recognize and target specific parts of HIV-1 known as Gag, Pol and Nef.

The STEP trial was conducted at 34 North American, Caribbean, South American and Australian locations where the HIV-1 subtype B was the predominant virus in the local HIV-infected populations. The trial enrolled 3,000 participants.

Preliminary tests indicated the vaccine was encouraging the appearance of the desired virus-attacking cells. More than 75 percent of vaccinated participants produced HIV-1 specific T-cells.

Nevertheless, this response to the vaccine did not predict protection. The trial failed. Immunizations were halted, Mullins recalled, after the first interim analysis indicated that the vaccine neither prevented HIV-1 infection nor reduced the load of virus in the body.

"Even though the T-cell responses were not sufficient to prevent infection," Mullins said, "we were interested in whether the vaccine-elicted T-cells had any impact on those strains of HIV-1 that established infections in the study subjects."

The research team tested for a "sieve effect," which, Mullins explained, occurs when a vaccine successfully blocks some strains of virus and not others. The researchers wanted to know, What are the genetic characteristics of those breakthrough viruses that slipped past the immunization barrier erected by the MRKAd5 vaccine?

The research team isolated strains of HIV-1 from both vaccine and placebo recipients in the study, and compared the genetic sequences of the strains. This would help researchers to determine if any changes in the "founder virus"—the virus first detected in the infection—might have helped it evade the vaccine-induced immune response and take hold in the vaccinated individuals.

The researchers identified potential T-cell targets in the protein-producing regions of the founder virus genetic sequences and compared these to the virus protein-targets of the vaccine—Gag, Pol and Nef. The researchers found that the distances for these viral genetic sequences were greater for the viruses taken from the vaccinated individuals, compared to those from the placebo recipients.

The most significant virus genetic site distinguishing vaccine from placebo recipients was in the region known as Gag-84, which was encompassed by several of the viral segments targeted by the vaccine.

Moreover, the researchers said that the extended divergence between the viruses from the vaccinated and the placebo groups was confined only to the sequences for the proteins targeted by the vaccine components (Gag, Pol and Nef) and was not found in other HIV-1 protein sequences. The influence of the vaccine on the virus genotype, Mullins said, was subtle.

Mullins and his team, as well as their collaborators from the STEP trials studies, are doing similar studies of the genetic impact of the Thailand vaccine RV144 on the AIDS virus. The RV144 vaccine was the first to show some probable effectiveness, but its efficacy was not great enough to put it to more general use.

The researchers added that their findings on breakthrough viruses suggest that new vaccines should be designed to put selective pressure on the virus in a controlled manner.

Such a vaccine, Mullins said, should select for genetic mutations in regions of the virus known to be associated with viral control and should avoid selecting for strains that can either escape the immune defense or act as decoys to fool the immune system.

The researchers propose a goal for new designs of vaccines aimed at inducing killer T-cell responses: corner the virus into assuming forms that debilitate it. This would make the infecting virus fitness-impaired—unable to adapt, reproduce in great numbers and cause disease progression.

"Despite the sad results of the STEP trial," Mullins said, "it has provided clues to ways for science to go forward in the search for an HIV vaccine. 3/29/11
Reference

HIV Enters and Injures Brain Early

SUMMARY: Structure and function changes in the brain are evident early in the course of HIV infection and are linked to inflammation, researchers reported at CROI 2011.

By Paul Dalton
Both clinical and laboratory research have shown that HIV injures the brain. As the focus of much research shifts to the long-term consequences of HIV infection, interest in the brain has grown. Several presentations at the 18th Conference on Retroviruses and Opportunistic Infections (CROI 2011) dealt with the effects of HIV on both brain structure and function.

Early Infection
In a talk titled "HIV Brain Viral and Inflammatory Signatures During Acute HIV infection," Victor Valcour of the University of California San Francisco (abstract 54) presented results from a study looking at measures of HIV and inflammation in the brains of people infected with HIV for less than 6 months. These individuals were compared to a matched group of chronically HIV infected people as well as a group of uninfected controls.

Results
- HIV was found in the brain of all participants.
- 50% of participants reported headaches during HIV seroconversion, although there was no correlation with levels of HIV in the brain.
- HIV levels were around 2.5 logs lower in cerebral spinal fluid (CSF) than in plasma.
- Several but not all makers of inflammation were higher in acutely infected people.
- This inflammatory pattern peaked during the second and third of four stages prior to seroconversion (called Freiberg stages).

This study shows that HIV is present at the earliest stages of HIV infection and leads to early inflammation in the brain. A better understanding of when and how HIV enters the brain should help both researchers and clinicians better deal with the effects of HIV on the brain.

Early Brain Changes
Ann Regin of Northwestern University in Chicago (abstract 55LB) presented results from the a study of the Chicago Early HIV Cohort Study, titled "Injury to the Brain Evident in Early HIV Infection."

This study followed 43 people living with HIV for less than 1 year and compared them to 22 uninfected individuals. Researchers looked at high-resolution images of the brain and measured gray matter volume in a number of brain regions.

Results
- Total gray matter volume was lower among people living with HIV than among uninfected people; this was true in both cortical and sub-cortical regions.
- Significant changes were evident in people infected for less than 6 months, and changes were seen in some people as early as 2 months.
- Overall, these changes were subtle, but the Regin speculated that they might progress over time.
- Preliminary results suggest people on antiretroviral therapy (ART) experienced lesser brain changes.

This study comparing brain structure of people newly infected with HIV to uninfected individuals shows that HIV injures the brain in the earliest phases of infection. The preliminary results showing a lesser effect in people on HIV treatment bolster the argument for early initiation of ART.

Brain Injury and Inflammation
Branford Navia of Tufts University in Boston (abstract 56) presented results from the HIV Neuroimaging Consortium, titled "Neurologic Injury on Stable ART."
This study followed 167 people living with HIV over a 2-year period at 7 sites in the U.S. Researchers looked at changes in cognitive function and their relation to both HIV treatment and various measures of HIV infection.

**Results**

- Declines in cognitive function increased by 13% after 1 year and 35% after 2 years.
- A CD4 count less than 350 cells/mm³ at the initiation of treatment was associated with increased risk of cognitive decline.
- Markers of increased inflammation were associated with decreased cognitive function.
- Age and length of time living with HIV were not associated with decline in cognitive function, however.
- Significant changes in brain structure were evident in people living with HIV.
- Low CD4 nadir (lowest ever count) was associated with a higher risk of brain injury.
- Progressive brain injury was associated with detectable HIV in the CSF, makers of immune activation, and time on ART.

This analysis shows that both neuropsychological function and brain structure are altered in people on stable antiretroviral treatment. Moreover, the risk of cognitive decline and brain injury were highest in people with the greatest level of immune deficiency and highest levels of inflammation and immune activation in the brain. Disappointingly, though, a greater amount of time on ART did not seem to reduce the risk of brain injury.

**HIV Genetic Diversity**

Finally, George Hightower of the University of California San Diego (abstract 57) presented results from the CHARTER Group, titled "Higher HIV Genetic Diversity is Associated with AIDS and Neuropsychological Impairment."

This study followed 187 people living with HIV, of whom 80 were men and almost 50% African American. Researchers measured levels of HIV genetic diversity and its effect on both rates of AIDS diagnosis and changes in neuropsychological impairment.

**Results**

- People with a high level of HIV genetic diversity in their plasma were 2.7 times more likely to have an AIDS diagnosis.
- Those with high rates of diversity in their CSF had similar (2.4 times) increases in rates of AIDS diagnoses.
- People with high rates of HIV genetic diversity in plasma or CSF or both also had nearly 2 times the amount of neuropsychological impairment.

This study suggests that a higher level of HIV genetic diversity is associated with an increased risk of both AIDS and neuropsychological impairment. Greater HIV genetic diversity has been associated with both longer length of time living with HIV and inversely with time on ART in other studies. These findings suggest that measuring HIV genetic diversity and strategies to reduce it might prove valuable in both predicting and intervening in neuropsychological impairment among people living with HIV.

Taken together, these studies present a sobering picture of the effects of HIV on brain function and structure. As people with HIV live longer, such effects become more important and research leading to a better understand of how to predict and affect HIV’s impact on the brain become more crucial.

**References**

Breastfeeding infants with HIV may develop drug resistance from ARVs in breast milk

Carole Leach-Lemens
Published: 31 March 2011

Early diagnosis and more regular testing during breastfeeding could reduce risk

Two thirds of breastfeeding infants infected after birth, born to mothers on antiretroviral therapy (ART), developed resistance to one or more antiretroviral drugs according to Clement Zeh and colleagues in a secondary analysis of the Kisumu Breastfeeding Study (KiBS) published in *PLoS Medicine* this month.

However, drug resistance appears to have developed as a result of exposure to antiretrovirals in breast milk or exposure to antiretroviral prophylaxis immediately after infection, not through transmission of drug-resistant virus from the mother.

Drug resistance mutations in HIV-infected infants developed between two weeks and six months after birth increasing over time: from 30% by week six, to 63% by week 14 and 67% by six months. No resistance was found among infants infected before two weeks of age or after six months when the mothers stopped ART and stopped breastfeeding.

The authors note this pattern suggests resistance was transmitted through exposure to maternal ART through breast milk, not through mother-to-child transmission (MTCT) of drug-resistant virus.

In resource-poor settings MTCT continues to cause significant death and disease. Approximately one-third of the estimated 450,000 children infected each year are infected through breastfeeding. Safe alternatives are often not feasible for the majority of women in such settings. The risks for infant death and disease linked to not breastfeeding are greater than the risks associated with HIV infection.

In these settings breastfeeding is the norm. Proven strategies to reduce the risks of MTCT through breast milk include giving mothers ART during the (recommended) six-month breastfeeding period. What happens is that maternal viral load in breast milk is reduced, and infants also get an indirect prophylaxis of ART through breast milk.

Studies have shown that antiretroviral drugs (including zidovudine, lamivudine, nevirapine and efavirenz) when given to nursing mothers are present in breast milk. However, antiretroviral drugs in breast milk can also have a negative effect for infants infected just before or during the breastfeeding period. Low levels of drug in the infant can encourage the evolution of drug-resistant virus if infection occurs despite prophylaxis.

The authors assessed this risk in a secondary analysis of the KiBS trial findings by looking at those infants who became HIV-infected during this time.

The parent trial, a single-arm open label prevention of mother-to-child transmission trial, looked at the safety and efficacy of giving zidovudine, lamivudine, and either nevirapine or nelfinavir to HIV-infected women from 34 weeks of pregnancy through six months of breastfeeding.

500 women were enrolled between July 2003 and November 2006 and gave birth to 502 infants. By the end of two years 32 (6%) infants were HIV-infected of which 24 (75%) were infected within the first six months of life.

Of the 24, nine were exposed to mothers on a nelfinavir-based regimen and the other 15 exposed to mothers on a nevirapine-based regimen throughout the breastfeeding period.

All nine (100%) of those exposed to a nelfinavir-based regimen and seven (47%) of those exposed to a nevirapine-based regimen developed drug resistance (95% CI: 28-78%, p=0.0095).

The most common mutations, M184V and K103N, conferred resistance to lamivudine and nevirapine, respectively.

All infants were given single-dose nevirapine within 48 hours of birth.

Blood samples from mothers and infants were taken at various stages and analysed for drug resistance.

None of the eight (of the 24 HIV-infected children) who were HIV-positive by two weeks of age had any signs of development of drug resistance. Similarly no mutations were seen in the eight infants infected after the breastfeeding period of six months.

Among the mothers of the 24 children the majority (84%) had no drug resistance mutations. Only one mother-child pair had overlapping mutation patterns that might imply the transmission of drug-resistant virus.

The authors note that the timing of the development of drug resistance suggests this happened either through single-dose nevirapine given to the infants or indirectly through ART in breast milk. Findings
from the SWEN study support this suggestion. (Infants given nevirapine prophylaxis while their mothers were on ART developed nucleoside reverse transcriptase inhibitor resistance in that study).

One major limitation, the authors note, is that HIV drug resistance genotyping was done on viral isolates from maternal plasma and not on breast milk isolates. In light of the increasing use of infant prophylaxis during breastfeeding, it is likely that drug resistance will be seen more frequently.

The authors suggest improved early infant diagnosis and treatment may help alleviate the problem. The authors conclude that close monitoring for the development of resistance in infants in PMTCT programmes who are exposed to ART through breast milk is needed, so that treatment can be tailored accordingly.

Reference


U.S. jury rejects Glaxo antitrust claims vs Abbott

Wed, Mar 30 2011
By Dan Levine

OAKLAND, California (Reuters) — A U.S. jury rejected GlaxoSmithKline's antitrust claims against Abbott Laboratories over allegations of unfair HIV drug pricing, after Britain's biggest drugmaker had asked for hundreds of millions in damages.

Glaxo accused Abbott of improperly hiking the price of one drug, Norvir, to help it preserve sales growth of one of its other HIV blockbusters, Kaletra.

The case had been in trial in an Oakland, California federal court, and the 10-member jury delivered its verdict on Wednesday.

The jury awarded Glaxo $3.4 million on its breach of contract claims. Abbott spokeswoman Adelle Infante said the company was considering an appeal of that finding.

"However, the jury's awarding of $3.4 million dollars in damages, instead of the $571 million that GSK was asking for, confirms our view that GSK's alleged damages were inaccurate and inflated," Infante said in an email.

Glaxo spokesman Marc Meachem said the company was disappointed that the jury did not agree on the magnitude of Abbott's conduct.

"We continue to believe that Abbott did not act in the best interest of those living with HIV," Meachem said, adding that Glaxo understood and accepted the jury's view.

Norvir plays a key role in AIDS-fighting cocktails because it can boost the effectiveness of other drugs. Glaxo accused Abbott of raising Norvir's price by 400 percent in 2003, as part of an effort to harm competitors whose drugs were dependent on being used in combination with Norvir.

The jury foreman, Michael Friedman, said Glaxo had not proven an essential element for antitrust damages: that a validly defined economic market existed for HIV booster drugs.

A Glaxo strategy document, which indicated that the company considered other non-booster drugs as competitors, hurt Glaxo's case, said Friedman, 63, a former attorney and self-employed life coach. "That was the most persuasive evidence for us," he said.

Several retailers which had been trying the case alongside Glaxo, including CVS Caremark and Safeway, settled with Abbott mid-trial for undisclosed amounts.

Had the jury awarded Glaxo antitrust damages, the amount likely would have been tripled. U.S. antitrust law calls for the scaling up of antitrust damages in the vast majority of cases.

The case in U.S. District Court, Northern District of California is SmithKline Beecham Corp, doing business as GlaxoSmithKline, v. Abbott Laboratories, 07-5702.

(Reporting by Dan Levine; Editing by Richard Chang and Tim Dobbyn)

U.N. Secretary-General Releases Report Assessing Global Response To HIV/AIDS

Nearly 30 years since researchers first described HIV/AIDS, U.N. Secretary-General Ban Ki-moon on Thursday in Nairobi, Kenya, released a report (.pdf) assessing the global HIV/AIDS response, Agence France-Presse reports (3/31).

According to a UNAIDS press release, the rate of new HIV infections has fallen by at least 25% over the past 10 years in 33 countries – including 22 in sub-Saharan Africa; more than six million people were
on antiretroviral treatment by the end of 2010; and services to prevent mother-to-child transmission of HIV reached more than half of those in need in 2009 (3/31).

However, the report notes, "These accomplishments, while promising, are insufficient and in jeopardy. Stigma, discrimination and gender inequality continue to undermine efforts to achieve universal access to HIV prevention, treatment, care and support. An unsustainable trajectory of costs and the effects of a global economic downturn combine to threaten progress" (3/28).

The report, "based on data submitted by 182 countries," offers five key recommendations to bolster the global fight against HIV/AIDS, the UNAIDS release states. These include efforts to: engage youth in "an HIV prevention revolution"; "[r]evitalize the push towards achieving universal access to HIV prevention, treatment, care and support by 2015"; promote HIV programs that are both cost-effective and cost-efficient; "[p]romote the health, human rights and dignity of women and girls; and ensure mutual accountability in the AIDS response to translate commitments into action" (3/31).

"World leaders have a unique opportunity at this critical moment to evaluate achievements and gaps in the global AIDS response," Ban said during the launch of the report, Deutsche Presse-Agentur/M&C reports. "We must take bold decisions that will dramatically transform the AIDS response and help us move towards an HIV-free generation," he added.

UNAIDS Executive Director Michel Sidibe, who joined Ban for the release of the report, added, "Thirty years into the epidemic, it is imperative for us to re-energise the response today for success in the years ahead" (3/31).

To meet the targets of "zero new infections, zero discrimination and zero AIDS-related deaths" by 2015 set on World AIDS Day 2010, Ban outlined several goals for member states, according to AFP (3/31). These include: reducing sexual transmission of HIV by 50 percent; ensuring that 13 million people receive HIV treatment; reducing TB deaths among people living with HIV/AIDS by 50 percent; eliminating mother-to-child transmission of HIV/AIDS; promoting education for children affected by HIV/AIDS; and reducing "the number of countries with HIV-related restrictions on entry, stay or residence" by 50 percent, the report states (3/28).

"As international funding for HIV assistance declined for the first time in 2009, the report [also] encourages countries to prioritize funding for HIV programmes, including low- and middle-income countries that have the ability to cover their own HIV-related costs," the UNAIDS release adds. "It also stresses the importance of shared responsibility and accountability to ensure the AIDS response has sufficient resources for the coming years," the release states (3/31).

Xinhua reports that the recommendations "will be reviewed by global leaders at a U.N. General Assembly High Level Meeting on AIDS, 8-10 June 2011" (Mutai, 3/31).

**A new signaling pathway of the immune system is elucidated**

**Results shed new light on chronic dermatitis**

A new signaling pathway, which is important for the regulation of the immune response and inflammation, was discovered by an international team of scientists led by prof Ivan Dikic from the Goethe University, Frankfurt, Germany. The scientists studied the involvement of ubiquitin, a universally present signaling protein in the cell. In today’s issue of the scientific journal "Nature" the scientists report a novel type of modified ubiquitin chains involved in regulation of various processes within the cell.

The researchers have shown that linear ubiquitin, where ubiquitin proteins are attached to each other in a head to tail fashion, regulates signaling cascades initiated by cytokine receptors at the cell membrane. Cytokines are essential for the proper immune response – e. g. tumor necrosis factor (TNF-alpha) alpha is released mainly by the macrophages and plays an important role in local and body-wide inflammation.

When a cytokine docks on the receptor of a cell, it induces a signaling cascade in many cell types, which transmits a signal to the nucleus – the DNA centre of the cell. After cytokine activation of its receptor, the linear ubiquitin ligase complex (LUBAC), which links ubiquitin into head-to-tail chains, is activated at the start of this cascade. This enzyme stimulates nuclear factor kappaB (NF-kappaB), which coordinates the expression of important genes for the immune response, including the production of antibodies. However, how the molecules of this cascade function in detail and which structures interact is still under investigation.

The Dikic group solved an integral part of this puzzle. Sharpin, a protein containing a Ubiquitin-like and Ubiquitin-binding domain (UBD), constitutes a key component of the linear Ubiquitin ligase complex. Using animal models, they show that a lack of Sharpin causes heavy inflammation of numerous organs and in particular the skin. This is characterized as chronic proliferative dermatitis with death of
keratinocytes, the predominant cells of the epidermis in charge of protecting the skin against environmental damage. This effect is dependent on the TNF signaling pathways.

The research reported allows us to reshape our thinking about how chronic proliferative dermatitis arises in humans, as well as opening new avenues of therapeutic intervention in the TNF-alpha signalling pathway. Moreover, a potential source of this disease may arise from mutations in a critical region of the linear ubiquitin ligase complex (LUBAC) allowing identification of patients that may respond well to targeted therapy. "In patients suffering from chronic proliferative dermatitis with unclear origin, it is now possible to specifically look for a mutation in LUBAC components", suggests Ivan Dikic.

**Scientists discover new drug target for inflammatory bowel disease: cytokine (IL-23)**

New research published in the Journal of Leukocyte Biology suggests that IL-23 helps regulate intraepithelial lymphocyte and natural killer cell immune responses in inflammatory bowel disease

A new discovery published in the April 2001 issue of Journal of Leukocyte Biology (http://www.jleukbio.org) raises hope that new treatments for illnesses like Crohn’s disease and ulcerative colitis are on the horizon. That’s because they’ve identified IL-23, a cytokine used by the immune system to ward off disease, as a major contributor to the inflammation that is the hallmark of these illnesses. With this information, it is now possible to develop new treatments that stop or reduce the damaging effects of IL-23, potentially bringing relief to millions of people with inflammatory bowel disease (IBD) and possibly other inflammatory illnesses as well.

"Our studies highlight the pathogenic role of IL-23 in the induction of mucosal injury in the gut," said Zhanju Liu, M.D., Ph.D., a researcher involved in the work from the Department of Gastroenterology at The Shanghai Tenth People’s Hospital at Tongji University in Shanghai, China. "Moreover, our work also provides a novel approach in the management of IBD and some autoimmune diseases."

To make this discovery, Liu and colleagues analyzed IL-23 expression in intestinal mucosa using laboratory techniques that amplify and simultaneously quantify a specific DNA molecule, allowing for both detection and quantification of one or more specific sequences in a DNA sample. IL-23R expression was detected in a variety of cells from peripheral blood and intestinal mucosa of IBD patients, suggesting that IL-23 plays an important role in the induction of proinflammatory cytokine secretion as well as different types of immune cells including recently discovered Th17 helper T cells that are often important in inflammatory diseases.

"This research is important because it helps us better understand why people develop IBD, and defines one of the key pathways driving the excessive inflammation," said John Wherry, Ph.D., Deputy Editor of the Journal of Leukocyte Biology. "Even more important, however, is that this study moves us a step closer to new treatments for these illnesses by targeting IL-23 and related proteins."

**Intelligent design: Engineered protein fragment blocks the AIDS virus from entering cells**

New research in the FASEB Journal suggests that a rationally designed HIV inhibitor could be used as basis for the development of effective new drugs to treat and prevent HIV/AIDS infection

In what could be a potential breakthrough in the battle against AIDS and a major development in the rational design of new drugs, scientists have engineered a new protein that prevents the virus from entering cells. This protein is based on a naturally occurring protein in the body that protects cells from viruses, except the man-made version does not cause inflammation and other side effects at the dosages needed to inhibit AIDS. This discovery was published in the April 2011 issue of The FASEB Journal (http://www.fasebj.org).

"This is science fiction made reality. These researchers took a protein apart and removed the portion that causes harm, then stabilized and modified the section that has a therapeutic effect," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. "Not only is this good news for people with AIDS, it’s good news for all of us as this research paves the way for similar work for many, many other illnesses."

The protein fragment is based on a naturally occurring protein called RANTES, which is part of the body’s immune system. RANTES naturally defends the body against HIV/AIDS, but cannot be used as a drug or drug candidate because it has several other biological effects which could cause harmful
inflammation. After examining the precise molecular structure of the RANTES protein, the researchers discovered that only a small fragment of the RANTES protein is actually responsible for blocking HIV entry into cells. From there, they dissected the desired section of the RANTES protein and worked to stabilize it without compromising its protective effects. After several sequential steps of molecular refinement and some virtual modeling, the researchers created a peptide with very high potency against HIV, with possible benefits for treating inflammatory diseases such as arthritis and lupus, as well as the prevention of transplant rejection.

"We're finally able to design smart anti-HIV drugs aimed at the right target. That's because scientists have spent decades figuring out the molecular details of how the virus enters cells, and the exact chemical structures involved," Weissmann added. "As the Renaissance sculptors wrought art from crude marble, today's molecular engineers today use intelligent design to create life-saving chemical masterpieces."

Researchers need to engage lesbian, gay, bisexual, and transgender populations in health studies
WASHINGTON — Researchers need to proactively engage lesbian, gay, bisexual, and transgender people in health studies and collect data on these populations to identify and better understand health conditions that affect them, says a new report from the Institute of Medicine. The scarcity of research yields an incomplete picture of LGBT health status and needs, which is further fragmented by the tendency to treat sexual and gender minorities as a single homogeneous group, said the committee that wrote the report.

The report provides a thorough compilation of what is known about the health of each of these groups at different stages of life and outlines an agenda for the research and data collection necessary to form a fuller understanding.

"It's easy to assume that because we are all humans, gender, race, or other characteristics of study participants shouldn't matter in health research, but they certainly do," said committee chair Robert Graham, professor of family medicine and public health sciences and Robert and Myfanwy Smith Chair, department of family medicine, University of Cincinnati College of Medicine, Cincinnati. "It was only when researchers made deliberate efforts to engage women and racial and ethnic minorities in studies that we discovered differences in how some diseases occur in and affect specific populations. Routine collection of information on race and ethnicity has expanded our understanding of conditions that are more prevalent among various groups or that affect them differently. We should strive for the same attention to and engagement of sexual and gender minorities in health research."

Because LGBT individuals make up a minority of the population, researchers face challenges in recruiting sufficient numbers of these individuals in general population surveys to yield meaningful data. Stigma experienced by gender and sexual minorities can make them reluctant to disclose their orientation, worsening the problem. Moreover, it is difficult to synthesize data about these groups when studies and surveys use a variety of ways to define them.

Because demographic data provide the foundation for understanding any population's status and needs, federally funded surveys should proactively collect data on sexual orientation and gender identity, just as they routinely gather information on race and ethnicity, the report says. Information on patients' sexual orientation and gender identity also should be collected in electronic health records, provided that privacy concerns can be satisfactorily addressed, the committee said. The National Institutes of Health should support the development of standardized measures of sexual orientation and gender identity for use in federal surveys and other means of data collection.

In addition, NIH should provide training opportunities in conducting research with LGBT populations. Training should engage researchers who are not specifically studying LGBT health issues as well as those who are. The agency also should use its policy on the inclusion of women and racial and ethnic minorities in clinical research as a model to encourage grant applicants to address how their proposed studies will include or exclude sexual and gender minorities.

Evolution: Not Only the Fittest Survive
ScienceDaily (Mar. 29, 2011) — Darwin's notion that only the fittest survive has been called into question by new research published in the journal Nature. A collaboration between the Universities of Exeter and Bath in the UK, with a group from San Diego State University in the US, challenges our current understanding of evolution by showing that biodiversity may evolve where previously thought impossible.

The work represents a new approach to studying evolution that may eventually lead to a better understanding of the diversity of bacteria that cause human diseases.
Conventional wisdom has it that for any given niche there should be a best species, the fittest, that will eventually dominate to exclude all others.

This is the principle of survival of the fittest. Ecologists often call this idea the ‘competitive exclusion principle’ and it predicts that complex environments are needed to support complex, diverse populations.

Professor Robert Beardmore, from the University of Exeter, said: "Microbiologists have tested this principle by constructing very simple environments in the lab to see what happens after hundreds of generations of bacterial evolution, about 3,000 years in human terms. It had been believed that the genome of only the fittest bacteria would be left, but that wasn't their finding. The experiments generated lots of unexpected genetic diversity."

This test tube biodiversity proved controversial when first observed and had been explained away with claims that insufficient time had been allowed to pass for a clear winner to emerge.

The new research shows the experiments were not anomalies.

Professor Laurence Hurst, of the University of Bath, said: "Key to the new understanding is the realization that the amount of energy organisms squeeze out of their food depends on how much food they have. Give them abundant food and they use it inefficiently. When we combine this with the notion that organisms with different food-utilizing strategies are also affected in different ways by genetic mutations, then we discover a new principle, one in which both the fit and the unfit coexist indefinitely."

Dr Ivana Gudelj, also from the University of Exeter, said: "The fit use food well but they aren’t resilient to mutations, whereas the less efficient, unfit consumers are maintained by their resilience to mutation. If there’s a low mutation rate, survival of the fittest rules, but if not, lots of diversity can be maintained.

"Rather nicely, the numbers needed for the principle to work accord with those enigmatic experiments on bacteria. Their mutation rate seems to be high enough for both fit and unfit to be maintained."

Dr. David Lipson of San Diego State University, concluded: "Earlier work showed that opposing food utilization strategies could coexist in complex environments, but this is the first explanation of how trade-offs, like the one we studied between growth rate and efficiency, can lead to stable diversity in the simplest possible of environments."

**Journal Reference:**
Robert E. Beardmore, Ivana Gudelj, David A. Lipson, Laurence D. Hurst. *Metabolic trade-offs and the maintenance of the fittest and the flattest.* Nature, 2011; DOI: [10.1038/nature09905](https://doi.org/10.1038/nature09905)