November 2012 Epidemics and AIDS Update

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1 November 2012

Shortly after HIV enters the body it infects cells of the immune system. As these infected cells are carried by the blood stream, HIV is spread throughout the body, including to the brain and spinal cord—the Central Nervous System (CNS). HIV does not infect brain cells, but it does infect cells of the immune system that travel to or are permanent residents of the brain. These HIV-infected cells release proteins and chemical signals that cause inflammation and impair the functioning of brain cells. If left untreated, HIV infection can eventually result in serious neurological issues—causing the brain to shrink, affecting clear thinking, bringing about difficulty controlling muscles and movement, degrading memory and key reflexes, and inciting changes to personality.

In high-income countries such as Canada, Australia and the United States and in regions such as Western Europe where potent combinations of anti-HIV therapy (commonly called ART or HAART) are widely available, severe HIV-related neurocognitive problems are no longer common compared to in the pre-HAART era. However, some research teams have reported that very mild neurocognitive impairment, detectable only with sophisticated and complex testing, appears to be relatively common among some ART users in the current era. The reasons for this are not clear but might be related to the following:

- aging of HIV-positive people
- possible impact of co-morbidities (such as cardiovascular disease, diabetes, hepatitis C co-infection) on the brain
- low-grade persistent inflammation in the CNS
potential neurotoxicity of ART
the inability of some anti-HIV drugs to enter or remain within the CNS

ART today
At present, ART generally refers to at least the following combinations of drug classes:
- two nukes + a non-nuke
- two nukes + a ritonavir-boosted protease inhibitor
- two nukes + an integrase inhibitor
When starting therapy for the first time, one of these combinations is usually prescribed. Among treatment-experienced patients, sometimes more complex regimens are used.

One type of simplification
Standard ART is expensive. Some doctors and their patients are also concerned about potential side effects from ART and would like to use fewer therapies. To try to find simpler regimens of anti-HIV drugs, researchers, mainly in Western Europe, have been conducting clinical trials of simplified therapy—particularly based on a protease inhibitor boosted with a small dose of ritonavir (Norvir). This is generally called protease inhibitor monotherapy (PI monotherapy).

The drugs most commonly used for PI monotherapy are as follows:
- darunavir (Prezista) and ritonavir
- lopinavir (in Kaletra; a fixed-dose combination of lopinavir and ritonavir)

In general, most clinical trials of PI monotherapy have found that such combinations are not as effective as standard triple therapy, the cornerstone of ART. However, in such trials when virologic failure occurred among participants given PI monotherapy, adding two nukes to their regimen was able to return HIV viral load to less than 50 copies/ml in 93% of cases.

Small and short
Based on published clinical trials so far, researchers estimate that the risk of PI monotherapy failing after one year is about 10%. However, it is important to bear in mind that most trials of PI monotherapy have had relatively small numbers of participants and did not last for more than one or two years. As a result, the overall long-term safety and effectiveness of PI monotherapy is not known.

Reports from Western Europe
Researchers in Sweden and Switzerland have been conducting clinical trials of PI monotherapy and HIV-related neurological research. Recently, two teams have separately reported that their data strongly suggest that injury to cells within the brain has occurred in some participants when exposed to PI monotherapy. The Swedish team recommends that PI monotherapy be used cautiously until further clinical trials are completed and more detailed information on the brain health of participants becomes available.

Sweden—Case 1
Doctors in Gothenburg reported details on two participants from a neurological study. As part of that study, participants had samples of their cerebrospinal fluid (CSF) taken from time to time. The CSF is the fluid that bathes the brain and spinal cord. The first participant was a woman who initiated ART in May 2007 when her CD4+ count was 170 cells and her viral load was 82,400 copies/ml. Her combination was as follows:
- AZT + 3TC (Combivir; a fixed-dose combination of these two nukes) and Kaletra
- After three months of this combination, her viral load in the blood fell to less than 20 copies/ml.
- In April 2009, her combination was changed to the following:
- abacavir + 3TC (Kivexa; a fixed-dose combination of these two nukes) and darunavir 800 mg and ritonavir 100 mg

In August 2009, her doctors discontinued Kivexa because of suspected abacavir skin rash and her regimen was reduced to the PI-based combination of darunavir-ritonavir.

Four months later, analysis of her blood found a viral load of 119 copies/ml and in the CSF the viral load was 709 copies/ml. Previously, when her regimen included Kivexa, viral load in the CSF was less than 20 copies/ml. Other abnormalities in her CSF included the following:
- elevated levels (10-fold) of lymphocytes
- elevated levels of beta_2_-microglobulin and neopterin – these chemicals are produced by the immune system when it becomes activated and inflamed in response to infections or tumours
- signals of injury to the brain cells
Collectively, all of these changes suggested that an infection was underway in the brain (tumours had been ruled out) and inflammation was occurring. All of this was likely due to resurgent HIV infection.

Doctors quickly added Truvada (a fixed-dose combination of two nukes: tenofovir + FTC) to her regimen. Within one month the viral load in her blood fell back to less than 20 copies/ml. Four months later when they performed another spinal tap, the viral load in her CSF had fallen to 56 copies/ml and inflammation was greatly reduced. Furthermore, there were no signals of injury to cells within the brain. The woman did not report any neurocognitive problems. However, formal assessments of her neurocognitive functioning were not performed.

**Sweden—Case 2**

The second patient initiated therapy in 2004 when his CD4+ count was 160 cells and his viral load was about one million copies/ml. His initial therapy also consisted of Combivir and Kaletra, which quickly suppressed his viral load in the blood to less than 50 copies/ml and raised his CD4+ count to 790 cells.

In 2007 he took part in a clinical trial where his therapy was intensified with the addition of two anti-HIV agents—the fusion inhibitor T-20 (enfuvirtide, Fuzeon) and the CCR5-co-receptor blocker maraviroc (Celsentri, Selzentry)—both for four weeks. After this he returned to his previous regimen.

In all cases, while he was on triple or greater anti-HIV therapy, the viral load in his CSF was less than 50 copies/ml. However, 12 months after changing his regimen to darunavir-ritonavir, the viral load in his CSF had increased to 478 copies/ml.

As with the first patient, during PI monotherapy elevated levels of lymphocytes, beta-2-microglobulin and neopterin were detected in his CSF. Also, signals of injury to brain cells were elevated.

Neurocognitive assessment done before and 12 months after changing to a simpler regimen of PI monotherapy did not find signs of decline. Like the case of the first patient, researchers did not find HIV that was resistant to treatment in his CSF.

When doctors added Kivexa to his regimen, within a month his viral load in the blood fell to less than 20 copies/ml and three months later the viral load in his CSF was also less than 20 copies/ml. Although the level of inflammation in the CSF had fallen, ongoing injury to brain cells was detected. The cause of this ongoing injury was not clear.

For purposes of comparison, the Swedish researchers analysed CSF samples from 21 participants who were receiving darunavir-ritonavir and two nukes. In only one of these 21 participants was there a signal suggestive of injury to brain cells.

**Assessing injury in the brain—NFL**

One marker, or protein, that is emerging as increasingly useful for assessing brain health is called NFL (neurofilament light protein). In general, NFL levels in the CSF are closely associated with injury to brain cells. Elevated levels of NFL have been found in HIV-negative people with dementia, multiple sclerosis, stroke and Alzheimer’s disease. One study in HIV-positive people found that increased levels of NFL in the CSF are associated with a high risk for developing HIV-related dementia.

**Assessing injury in the brain—S100B**

Astrocytes are cells that help maintain the health of the brain and also assist brain cells to communicate. Researchers have found that astrocytes can release a protein called S100B. At low levels, S100B helps the development of brain cells. However, at high concentrations it can cause brain cells to die. One study in HIV-positive participants linked elevated S100B levels in the CSF to an increased risk of death among people with dementia. In another study, elevated S100B levels were linked to neurocognitive dysfunction in HIV-positive people.

**Results from Switzerland**

In Switzerland, researchers have been conducting a clinical trial of Kaletra monotherapy versus ART. Prior to entering this study (called MOST), participants had been taking ART for at least four years, their CD4+ counts were between 450 and 500 cells and viral loads were less than 50 copies/ml.

The MOST study was prematurely stopped because six out of 42 participants (14%) who were taking Kaletra monotherapy had viral loads in the blood that rose and remained above 400 copies/ml. Researchers considered those six participants to have virologic failure. This was in contrast to the comparison group in MOST who took ART and in whom no virologic failures occurred.

**A note about assessing neurocognition in MOST**

Since specific neurocognitive testing to assess very subtle changes (such testing follows a protocol called the Frascati criteria) was not performed in MOST study subjects, including those with elevated viral load in their CSF, it is not possible to be certain whether any of them had HIV-associated neurocognitive disorders. Nevertheless, researchers found that none of them showed any obvious signs of major cognitive disorders.
Out of the six participants whose regimen failed, CSF samples from five were available for analysis. In all five cases, virologic failure occurred in CSF. Also found in these five participants’ CSF samples were higher-than-normal levels of neopterin (suggestive of immune activation) and S100B, suggestive of injured astrocytes.

Although extensive neurocognitive testing was not done in MOST, doctors found that none of the participants with elevated viral load in their CSF showed any obvious signs of moderate to severe neurocognitive impairment.

**No treatment failure but hints of central nervous system injury**
Swiss researchers analysed 65 CSF samples (34 on ART and 31 on PI-monotherapy) from 49 HIV-positive patients enrolled in MOST. They found that, in the CSF of PI-monotherapy patients, concentrations of S100B (suggestive of injured astrocytes) and neopterin (suggestive of immune activation) were significantly higher than in patients on ART.

Other key findings from the CSF analyses in MOST were as follows:
- The CSF from four participants whose regimen (PI-monotherapy) failed had the highest levels of S100B and neopterin.
- The researchers also found that, even in participants on PI-monotherapy who had no evidence of viral failure either in the blood or in the CSF, S100B levels were higher than in the CSF of participants on ART.

Furthermore, six of 17 participants (35%) taking PI-monotherapy whose regimen was not failing, but only one of 32 (3%) participants on ART (who also was not failing) had elevated levels of S100B in their CSF, specifically S100B values higher than 1,000 picograms/ml. Whether this cutoff may serve to identify patients with suboptimal antiretroviral treatment needs to be confirmed in future studies designed specifically for this purpose.

The Swiss analysis of CSF is important as it suggests that “undetectable viral load in the [blood] and the CSF do not necessarily rule out ongoing inflammation in the brain.” Moreover the Swiss team notes that their findings suggest that monitoring the health of astrocytes may be important because damage to astrocytes (using markers such as S100B) may be an early signal of inflammation within the brain.

Researchers at Harvard University have also found that despite effective ART, inflammation in the CSF of HIV-positive people could still be detected.

**Monkey research**
Other researchers have found ongoing inflammation in experiments on monkeys despite the animals being given potent combinations of anti-HIV drugs. Specifically, researchers used monkeys susceptible to SIV (simian immunodeficiency virus), a virus closely related to HIV that causes an AIDS-like disease in these animals. The researchers found that viral load in the blood and CSF can fall to undetectable levels when the animals are treated. Yet, when analyzing the CSF samples of treated animals, researchers found that inflammation was still occurring.

**Putting it all together**
The research with HIV-positive people in Sweden, Switzerland and the U.S., together with experiments on monkeys with SIV, suggests that inflammation in the brain is a problem with these infections and that such inflammation might not fully resolve despite treatment. This suggests that caution should be exercised with PI monotherapy.

It also suggests that further research is needed with ART users so that neuroscientists can explore the cause of ongoing inflammation in the CNS and ways of dealing with this, particularly as HIV-positive people age.

**Moving away from monotherapy to dual therapy**
Some clinical trials of simplified therapy have been completed or are underway. Hopefully these other studies will also investigate the possibility of any changes in the brains of participants.

Some examples of internationally run clinical trials of simplified regimens planned, underway or completed include the following combinations:
- atazanavir + Kivexa
- darunavir + maraviroc
- Kaletra + 3TC (lamivudine)
- Kaletra + raltegravir (Isentress)
- maraviroc + raltegravir

**Resources:**
- A mind of her own – understanding and dealing with HIV-related neurocognitive issues
Jury convicts ‘poz vampire’ Boone of attempted murder
By Andrew Seymour, Ottawa Citizen October 31, 2012

OTTAWA — A self-described “poz vampire” who had unprotected sex with other men without telling them his HIV positive status has been found guilty of trying to kill his sex partners with the disease.

“There is no way I was trying to kill anyone,” a shaking Steven Boone told his lawyers before being led sobbing from the prisoner’s box in shackles.

Boone’s mother broke down in tears in the hallway after the verdict late Wednesday. Inside the court, she yelled at a Crown attorney observing the proceedings who she thought was smiling.

“What are you smirking about? You think it’s funny?” she asked.

Moments earlier, Boone could be seen becoming emotional as the jury found him guilty of three counts of attempted murder and administering a noxious substance — his semen — on three young men, including a 17-year-old, with whom he’d had unprotected sex. The 17-year-old male later tested positive for HIV.

Boone, 31, was also convicted of three counts of aggravated sex assault. Two of the charges related to two of the men he was convicted of trying to kill. The third count was in relation to a man who he had sex with using a condom.

The jury acquitted him of two counts of aggravated sexual assault in relation to two men who engaged in oral sex with him. Boone told none of the men he was HIV positive.

The guilty verdict signalled that the jury felt there was a realistic possibility of transmission of HIV, even during anal sex using a condom. What wasn’t clear was if they concluded Boone had ejaculated in or damaged the condom, which would increase the risk of spreading the disease.

They also concluded the Crown had proved there was an intent to kill three men Boone had unprotected sex with.

However, the jury’s not guilty findings on two of the aggravated sex assault charges mean they didn’t find there was a realistic possibility of the transmission of HIV during oral sex where no ejaculation occurred.

What constitutes a “realistic possibility” of HIV transmission was the central issue in the trial.

Canadian law says you don’t have to disclose your HIV positive status if there isn’t a realistic possibility of transmitting the disease.

The Crown argued that oral sex with an HIV positive person with an unreduced viral load represented a greater risk than unprotected vaginal sex with someone who had a low viral load.

A Supreme Court of Canada decision on the eve of Boone’s trial found that unprotected vaginal sex with a person with a low viral load met the standard of a “realistic possibility” of transmitting the disease and required disclosure.

Vaginal sex where the HIV-positive person uses a condom and has a low viral load didn’t require disclosure, according to the Supreme Court of Canada decision.

An HIV expert who testified for the Crown concluded the risk in Boone’s case for oral sex without ejaculation was about 1 in 2,000. The risk of transmitting HIV during sex with a condom where there was no ejaculation was about 1 in 1,000, the doctor concluded. Boone’s viral load was considered about average.

An expert who testified for the defence wouldn’t put a number on the risk of transmission from oral sex, but opined it was so close to zero it was almost theoretical.

To secure the attempted murder convictions, the Crown relied extensively on sexual chats where Boone often boasted about having unprotected sex with unsuspecting sex partners and teenage virgins.

In his quest to convince people to have “bareback” sex, Boone would claim condoms caused cancer and portrayed life with HIV as something that increased your sex drive.

Boone said he “lost count” of how many HIV negative men he had sex with without telling them he had HIV.

The Crown alleged Boone was part of a disturbing subculture of “bug chasers” who would try to “stealth poz” HIV-negative men in an attempt to give them the disease.

When confronted about his HIV-positive status, Boone often claimed he just found out he had the disease and just didn’t know how to disclose it. The crimes he was convicted of occurred between December 2009 and April 2010 — he found out he was HIV positive in October 2009.

Boone’s lawyers argued that the “needy” Boone was simply looking for love with the men, and was more interested in dating them than killing them.
The online sex chats were just “a lot of charged up fantasy talk,” said lawyer Ian Carter. Boone’s online bravado occasionally gave way to what appeared to be his real feelings about the disease.

Boone lamented how he made the “ultimate sacrifice” by becoming infected only to be dumped by his ex-fiancé once his conversion was complete.

“I risked everything ... EVERYTHING ... and i got nothing but a disease that causes most guys to turn away from me,” Boone wrote in the days before he was arrested. “I’m tired of being cast as the villain. I’m tired of people seeing me as someone who is trying to cause harm to others.”

While the jury’s verdict brought to a close this trial, Boone’s legal troubles are far from over. It’s now expected the Crown will seek a dangerous offender designation for Boone, which, if successful, could see him locked up indeterminately.

He will also stand trial starting Nov. 13 on separate charges of attempted murder, attempted aggravated sex assault, sex assault and a breach of probation involving a developmentally delayed man in his early 20s, who functions at the level of a 13-year-old.

Boone will then stand trial in December along with another HIV-positive man on allegations of aggravated sexual assault on two men in Waterloo Region.

**Many HIV Patients Skip Medications to Drink**

*Reuters Health*, (11.01.2012) Kerry Grens

Researchers have shown that about half of HIV patients on antiretroviral therapy skipped their medicines when drinking alcohol. Seth Kalichman, professor at the University of Connecticut, and colleagues investigated how patients’ beliefs about drinking and taking medication might contribute to poor treatment adherence. They surveyed 178 patients (four out of five were men) who drank alcohol and were being treated with antiretroviral drugs. The researchers asked participants about their alcohol-related beliefs, and whether people should not take both drugs and alcohol at the same time by avoiding either alcohol or the medicines. Over a year, the team checked with patients every month to determine how well they were adhering to their treatment using a pill count, and every other month they enquired whether the patient had been drinking recently. Doctors’ offices provided the patient’s level of virus in the body and CD4-cell counts.

Results showed that 51 percent of patients avoided medications when they drank, and half of this group had poor adherence to prescriptions. The half of the group that skipped pills also said they did not take medication until the alcohol is completely out of their system. Of those who reported not skipping their medications when they drank, 36 percent did not adhere well to prescriptions and 31 percent said they did not take medication until the alcohol is out of their system. People who skipped medications while drinking were more likely to have higher levels of HIV in their system and lower numbers of CD4 cells.

The authors concluded that patients living with HIV who deliberately stopped treatment when they are drinking are at risk for treatment failure. Kalichman suggested a simple fix, educating patients about drinking and HIV treatments.

The study titled, *Intentional Non-Adherence to Medications among HIV Positive Alcohol Drinkers: Prospective Study of Interactive Toxicity Beliefs*, was published online in the *Journal of General Internal Medicine* (2012, DOI: 10.1007/s11606-012-2231-1).

**Denmark: Late HIV diagnosis not a major factor in continued spread of HIV**

Michael Carter

Published: 05 November 2012

Individuals whose HIV infection is diagnosed late are making only a minimal contribution to the HIV epidemic, Danish investigators report in the online edition of the *Journal of Acquired Immune Deficiency Syndromes*. Using phylogenetic analysis, researchers were able to trace transmission clusters. Only 20% of people diagnosed late were located within such a cluster.

However, the study’s findings provide further evidence that people who have only recently been infected with HIV are largely sustaining the spread of HIV. Almost all the transmission clusters identified by the investigators involved young gay men, many of whom had primary HIV infection.

HIV incidence has been stable in Denmark over the past 20 years. There are approximately 300 new infections each year in the country. Several studies have now shown that the majority of onward HIV transmissions originate in individuals with undiagnosed infection. However, the contribution of individuals whose HIV is diagnosed late (with a CD4 cell count below 200 cells/mm³) is currently unknown.
Investigators therefore conducted a study involving the 1515 people newly diagnosed with HIV in Denmark after 2001. Using a technique called phylogenetic analysis, the authors looked at networks and clusters of HIV transmissions to see if they could identify the factors that are driving the HIV epidemic in the country.

Approximately a fifth (260) of people were found to have primary HIV infection and 460 individuals were diagnosed late. A total of 696 infections involved gay men.

The investigators identified a total of 46 transmission clusters involving 502 people.

“We found one third of the sequences from newly diagnosed, treatment naïve patients formed 46 different phylogenetic clusters visualising potential local epidemics,” comment the authors.

People within transmission clusters had a significantly higher CD4 cell count (402 vs 287 cells/mm$^3$, $p < 0.001$) and higher viral loads (63,000 vs 25,000 copies/ml, $p < 0.05$) than individuals who could not be placed within transmission networks.

Half of all people with primary HIV infection could be placed within a cluster, compared to only 22% of people whose HIV was diagnosed late.

“Individuals presenting with low CD4 T-cell counts contribute less to the epidemic than individuals with higher CD4 T-cell counts,” observe the researchers.

Age under 30, injecting drug use, primary infection and sex between men were all significantly associated with being in a cluster ($p < 0.001$).

Some 40 clusters involved gay men, and the two largest transmission networks involved half of all people with primary infection.

“Within 46 clusters we found primary HIV sequences more frequently in larger clusters,” comment the investigators. They believe this is “compatible with the increased infectiousness and transmission potential...ascribed to primary HIV infection”.

Several of the clusters spanned the full study period, “an explanation for the constant level of HIV diagnoses in Denmark”.

The study’s findings have implications for HIV prevention. The authors recommend that efforts should be targeted at younger gay men, especially those at risk of having primary infection. “Very late presenters do not seem to be of significant importance from the transmission standpoint. Efforts to identify very late presenters should be enhanced for the benefit of the individual patient.”

Reference

November 2, 2012

**Brief Treatment Interruptions for Cure Studies Are Safe, Well-Tolerated**

A new study has shown that short treatment interruptions of antiretroviral (ARV) regimens are both safe and well-tolerated among people with HIV. This is good news for scientists pursuing functional cures because they can use such windows to study novel agents that would suppress the virus without an ARV regimen. University of Minnesota researchers presented their findings as a poster abstract at the IDWeek 2012 meeting in San Diego. They studied 14 HIV-positive people with a CD4 count above 350 and an undetectable viral load, all of whom were on stable ARV regimens. After stopping the subjects’ HIV medications, the researchers carefully monitored their CD4 counts and viral loads until HIV RNA was detectable in the blood, at which point the researchers took samples of the HIV reservoir, performed a genotyping test and then reinitiated ARVs. The average study participant took two weeks to reach a detectable viral load and another two weeks to reach full viral suppression once again. All subjects reached virologic suppression. None saw their CD4 levels change significantly; none suffered physical symptoms with the viral load’s return; and none developed drug-resistance or experienced virologic failure.

**Death rates elevated at all CD4 counts below 500 in sub-Saharan Africa**

Keith Alcorn
Published: 06 November 2012

An analysis of death rates between the HIV-positive and HIV-negative partners in serodiscordant couples in sub-Saharan Africa has found significantly higher death rates in people with HIV with CD4 counts below 500, suggesting that expanding treatment beyond eligibility thresholds of 200-250 would have a substantial impact on mortality.
The findings come from an analysis of survival, in couples recruited into the Partners in Prevention study of acyclovir secondary prophylaxis in HIV/HSV-2 co-infected people in order to prevent HIV transmission to their HIV-negative regular partner.

Current World Health Organization guidelines recommend that antiretroviral treatment should be provided to all people with HIV who have CD4 cell counts below 350, although this recommendation has not been adopted in all low- and middle-income countries.

Since these guidelines were issued in 2010, the HPTN 052 study of early antiretroviral treatment for prevention of HIV transmission in serodiscordant couples has demonstrated a significant reduction in the risk of severe bacterial infections, WHO stage IV clinical events, tuberculosis or death. However data presented at two successive international conferences have shown that this reduction is attributable to a reduction in extrapulmonary TB cases and is not evident across other categories.

Other data to inform guidelines are needed, so the trial investigators carried out an analysis of mortality by CD4 count stratum and viral load in the Partners in Prevention study population. In particular, investigators wished to determine whether people with HIV were at increased risk of death at higher CD4 cell counts when compared to their HIV-negative partners, who lived in the same household or neighbourhood and might be exposed to the same environmental factors for disease, the same diet and the same access to health care.

The analysis looked at death rates in 3295 serodiscordant couples in seven sub-Saharan African countries, followed for a median of 20 months. Participants with HIV had a baseline CD4 cell count of 250 or above and participants already diagnosed with an AIDS-defining illness were excluded from the study. Antiretroviral therapy was provided during the study according to local criteria.

The median CD4 count of partners with HIV at enrolment was 426 in men and 481 in women; by the final visit the median CD4 count had declined to 394 in men and 437 in women, and approximately one-quarter had some HIV-related symptoms during the follow-up period (approximately ten per cent started antiretroviral therapy during the study).

One hundred and nine deaths were recorded, 74 in people with HIV and 25 among uninfected persons. Information on causes of death is limited due to incomplete reporting and should be treated with caution, but people with HIV infection were more likely to die of pneumonia, gastrointestinal or other infections (including malaria).

Excess deaths in the partners with HIV were most frequent in those with CD4 cell counts below 250 (29.3 per thousand person-years of follow-up) but were significantly higher in all CD4 cell count strata below 500 when compared to HIV-negative partners.

Univariate Cox regression analysis showed a significantly higher rate of death in partners with HIV with CD4 cell counts in the 350-499 range (HR 2.7, 95% confidence interval 1.2-5.6, p = 0.013) but multivariate analysis which controlled for CD4 cell count, viral load above 100,000 copies/ml, antiretroviral use and WHO HIV disease stage showed an elevated hazard ratio of borderline significance (aHR 2.2, 95% CI 1.0-4.9, p = 0.053).

But after adjustment for antiretroviral therapy use, the rate of excess mortality per thousand person-years was highly significant in this CD4 stratum (8.9 per 1000 person-years, compared to 15.2 in the 250-349 stratum and 29.3 in the <250 stratum) (all p < 0.001).

Viral load above 100,000 copies/ml was also associated with a significantly higher rate of excess deaths (43 per thousand person-years, p < 0.001).

The authors also calculated the number of people who would need to be treated with antiretroviral therapy in order to prevent one death, a measure which can give some indication of the resources that need to be utilised in order to achieve a desired outcome, in this case the prevention of deaths.

One hundred and thirteen people with CD4 counts in the 350-499 range would need to be treated for a follow-up period of 20 months to prevent one death, compared with 66 people in the CD4 range 250-349 and 34 people with CD4 counts below 250.

However, this analysis only looks at the benefit of treatment to the persons treated, and not at the potential effect of treatment on onward transmission.

The authors conclude that their data “support increasing the CD4 threshold for treatment initiation, together with expanding HIV testing for asymptomatic persons in the community.”

Reference
De Bruyn G et al. Mortality in members of HIV-1 serodiscordant couples in Africa and implications for antiretroviral therapy initiation: Results of analyses from a multicenter randomized trial. BMC Infectious Diseases 12: 277, 2012. (View the full-text article here).
Suze Randall and Humphry Knipe, a British married couple, are Southern California pornography pioneers.

Ms. Randall, 66, a former nurse and fashion model, shot nudes for The Sun’s Page 3 girl feature and became the first female staff photographer at Playboy and, later, Hustler.

She switched to 16-millimeter films and now has a well-known hard-core Web site, Suze.net. Mr. Knipe, a writer, is her business manager. Their daughter Holly is part of the business, too. Last month, she directed a pornographic film on their remote ranch in the hills above Malibu.

They remember the torrent of fear when performers began dying of AIDS in the 1980s.

“It was petrifying,” Ms. Randall said. “You didn’t want to be responsible for someone making love and then dying a lingering death. It took all the fun out of it.”

The first AIDS test was released in 1985, and the industry adopted it, but not very effectively.

“We had the ‘Blood Truck’ at casting calls,” Mr. Knipe said. “It was an ambulance that drew blood. But you’d have to wait two weeks for results.”

Worse, early tests were for antibodies to the virus that did not develop for months after an actor would have already been infected.

Heterosexual performers knew the disease was mostly among gay men and drug addicts, but actors who did both gay and straight films worried them. John C. Holmes, for example, the most famous male actor of that era, also did some gay films. He was given an AIDS diagnosis in 1985, withered away to 90 pounds and died three years later.

“We’re a small, very gossipy industry,” Mr. Knipe said. “If the word got out that a guy was bi or did drugs, no girl would work with him.”

Some producers, the couple included, stopped filming penetration scenes.

Some actors changed what they would do.

Nina Hartley, a registered nurse and an actress since 1984, said she has not let a male co-star ejaculate inside her since 1986.

“Just too risky,” she said.

Pornographic films typically end with ejaculation on the actress’s skin; while feminists find that demeaning, Ms. Hartley said, she credited that “trope” with saving dozens of lives between 1984, when AIDS first entered the talent pool, and 1998, when industry-regulated testing was imposed.

That year, 1998, saw the industry’s worst scandal. Until then, producers accepted test results on paper from many doctors. Then one woman after another suddenly began testing positive for H.I.V. Sharon Mitchell, a former actress with a doctorate in human sexuality and training in taking blood samples, was hired by the industry to investigate. She figured out that all eight women had done anal sex scenes with an actor named Marc Wallice — someone she herself had once worked with.

In an interview, Dr. Mitchell said she got one of Mr. Wallice’s producers to entice him to his office with an offer of $10,000. “And then we kind of kidnapped him and I took his blood,” she said. “It came back with a very high viral load.”

At a news conference at the Adult Industry Medical clinic in Sherman Oaks, Calif., which she started with support from the industry, she named Mr. Wallice as the likely “patient zero.” In interviews he gave at the time to industry publications, Mr. Wallice denied accusations that he had changed a positive result from an obscure Burbank clinic to a negative.

Studios switched to condoms-only shoots for a while, but dropped that as Dr. Mitchell’s clinic ramped up testing. It eventually did 1,200 tests a month, and had a database on which producers could check results.

She remembers testing Darren James in 2004, just after he had returned from performing in Brazil, and again 26 days later. The first was negative, but she said he looked unwell. “I told him, ‘Please don’t work,’ ” she said. “But he did internal ejaculations with 13 women. When I heard that, I knew there would be three to five positives, and there were three.”

Those were the industry’s last confirmed transmissions. Mr. James has since endorsed the campaign to make condoms mandatory on the sets of pornographic films.

Then, last year, the clinic’s database was hacked; the medical records, names and addresses of hundreds of performers were posted online, creating a furor. Actors threatened to sue for invasion of privacy, and the state ordered Dr. Mitchell to get a new clinic license. Instead, she closed down.
In January, the industry created a new system, overseen by an infectious disease specialist, Dr. Peter Miao. It certifies which labs may do tests, and its database has only two bits of information: a green check indicating a negative test in the last 14 or 28 days, or a red X telling producers the actor is unavailable. (Actors can make themselves unavailable for any reason, including vacation.) The new tests pick up H.I.V. and syphilis within 14 days of exposure.

“That’s not perfect, of course,” Dr. Miao said. “But it closes the window a lot.”

**AIDS Research And Human Retroviruses Journal Publishes Special Issue On Prevention**

The journal of AIDS Research and Human Retroviruses has published a special issue examining the "complex factors involved in the sexual transmission of HIV, the urgent need for new preventive approaches, and the most promising methods currently in development,” according to a press release from the publisher, Mary Ann Leibert, Inc. "It is currently an exciting time in HIV prevention science research, with progress on multiple fronts,” Thomas Hope, editor-in-chief of AIDS Research and Human Retroviruses and professor of cell and molecular biology at the Feinberg School of Medicine, Northwestern University, said in the press release. The entire issue is available online (11/5)

**The Phosphorus Index: Changes afoot**

Phosphorus (P) is both an essential nutrient in agricultural fields and a contributor to poor water quality in surface waters. To encourage improved P management in fields, the P Index was proposed as a risk assessment tool in 1992. After 20 years of use, modifications, and growing pains, does the P Index accurately assess the risk of P loss?

A special section being published next month in the Journal of Environmental Quality addresses that question. The collection of papers grew out of a symposium at the American Society of Agronomy, Crop Science Society of America, and Soil Science Society of America 2011 Annual Meetings. The section acknowledges the problems that have been encountered with P Index development and implementation, such as inconsistencies between state indices, and also suggests ways in which the indices can be tested against data or models to improve risk assessment and shape future indices.

The P Index was proposed in a 1992 symposium after people became aware of the environmental impacts of P loss from fields. Many farmers were applying manure or other biosolids to their fields at rates that over-applied P. Researchers realized that assessing the risk of P loss from those products was important to protect water quality. The P Index tool was needed to connect various conditions because P loss is influenced by both site characteristics (e.g., soil test levels, connectivity to water) and the sources of P applied (e.g., inorganic fertilizer, organic sources). It was therefore a great improvement over the use of agronomic soil testing for P risk assessment.

"The objective of the original P Index was to identify fields that had high risk of P loss and then guide producers' decisions on implementing best management practices," says Nathan Nelson, ASA and SSSA member and co-author of the special section's introductory paper. "The P Index has developed into a widely used tool to identify appropriate management practices for P application and fields suitable for such application."

The original 1993 paper by Lemunyon and Gilbert laid out three short-term objectives for the P Index: 1) to develop a procedure to assess the risk for P leaving a site and traveling toward a water body; 2) to develop a method of identifying critical parameters that influence P loss; and 3) to select management practices that would decrease a site’s vulnerability to P loss.

These objectives were to be met using fairly simple calculations that took into account both source factors and transport factors. Source factors included levels of P in the soil, rates of P fertilization, and methods or timing of P addition. Features such as soil erosion, runoff, and distance to streams composed the transport factors.

"P loss is high when you have both a lot of P present and an easy transport pathway,” explains Nelson. "The index has been designed to evaluate the interaction between these different factors."

Because the P Index can be used to guide conservation practices, the USDA-National Resource Conservation Service (NRCS) adopted it as part of their management planning process. The NRCS, then, left it up to each state to develop their own P Index best suited for their environments and concerns.

"The P Index was meant to be something that could be easily computed with readily available data, so an NRCS agent would be able to obtain the necessary inputs,” says Nelson. "But there are many different factors that influence P loss as you move from one physiographic region to the next. The differences in
transport processes, soils, and landscapes in each state have led to 48 different versions of the P Index, and some of them are very different."

The inconsistencies of indices across states, along with a perceived lack of improvement in water quality in some regions, are now bringing the accuracy of the P Index into question. With different calculations in place, a set of factors may be categorized as low risk in one state and medium, or even high, risk in another. These discrepancies become especially obvious along state borders.

Researchers understand the need to improve P indices and have made it a priority to base any changes on sound scientific data. Efforts to preserve, evaluate, and improve the P index led the NRCS to release a Request for Proposals within the Conservation Innovation Grant Program. Three regional efforts were funded to evaluate and improve the indices in the Heartland, the Southern State, and the Chesapeake Bay regions of the U.S. Additionally, a national coordination project and two other state-level efforts (Ohio and Wisconsin) were recently funded through the Conservation Innovation Program.

While the final suggestions for the next generation of the P Index are likely a few years off, the research is currently underway. Due to variations in regional characteristics and the problems previously encountered by state boundaries, it is likely that suggestions for improved indices will be based on regional distinctions, Nelson says. The objective is that the evaluations will lead to optimized P indices and better management tools that accurately incorporate site and source characteristics to predict the risk of P loss from fields.

"The scientific community backs the P Index as the best method to assess P loss risk," says Nelson. "The challenge now is to develop consistency in P indices across state boundaries and quantify the accuracy of P index risk assessments."

**Researchers discover immune pathway**

**Discovery from Aarhus University maps an important pathway in the first line of the immune defence—In the longer run, this discovery may have implications for the treatment of stroke and cancer patients**

Researchers from Aarhus University, Denmark, have now discovered an important mechanism behind one of our most fundamental lines of immune function. The discovery has been published in the esteemed scientific journal, *The Journal of Immunology*, where it has been highlighted as a top story.

In collaboration with colleagues from USA and Turkey, they have discovered exactly which enzymes collaborate in the first line of the immune defence. Thus, they answer a central question about the so-called complement system, which has been a focal point of the scientific field for the past decade: which enzyme does what?

Using blood samples from a unique patient harbouring a rare genetic syndrome, the researchers from Aarhus University have now established that it is the enzyme MASP-1 that is key to the activation of the complement system.

"Understanding the immune system is a central goal in itself in scientific terms, especially for our research group conducting basic research. But in the longer run, it is also an important goal that this knowledge may help people and cure diseases", says postdoc Soeren Egedal Degn from Aarhus University, who is first author on the paper.

**Big perspectives for patients**

He believes that once one has defined how the complement system works, it will be possible to manipulate it: "For example this system is important for the survival of patients undergoing chemotherapy, because this treatment suppresses other functions of the immune system—so in their case it is beneficial to "rev up" the system. But following a heart attack there may be reasons to instead dampen the system. The complement system has an unfortunate tendency to attack tissues that have suffered damage due to deprivation of oxygen, and thereby it exacerbates the damage already done to the heart", says Soeren Egedal Degn.

He notes however, that the new discovery is unlikely to result in concrete new treatment modalities in this decade.

**MASP-1 and the lectin pathway**

Behind the discovery of the central role of MASP-1 in the complement system is, apart from Soeren Egedal Degn, also the Aarhus professors Jens Chr. Jensenius and Steffen Thiel, who are considered international experts in the field. They have previously discovered the four other known proteins related to MASP-1, namely MASP-2, MASP-3, MAp19 and MAp44. Together, these proteins make up a central part of the activation pathway of complement known as the lectin pathway. The research group in Aarhus,
which also includes the laboratory technicians Lisbeth Jensen and Annette G. Hansen, has been central in the elucidation of the lectin pathway through the past 15 years.

The enzyme MASP-1 is able to efficiently auto-activate, for example when it "senses" a bacterium. It then activates MASP-2, which in turn activates the rest of the complement system in a cascade-like manner, where a long list of enzymes sequentially activate each other—much like dominoes. The result is a signal to immune cells to home to the area in the body, where the system is activated, and to kill the intruding bacteria. The bacteria are also covered in "molecular tags", making it easier for the immune cells to recognize and efficiently engulf them. Finally, the complement system directly "punches holes" in the bacteria, by forming pore-like structures in their membranes.

New bacteria to fight against intestinal inflammation

This protection is provided by a human protein, Elafin, which is artificially introduced into dairy produce bacteria (Lactococcus lactis and Lactobacillus casei). In time, this discovery could be useful for individuals suffering from chronic inflammatory diseases such as Crohn’s disease or ulcerative colitis. The results of this research were published in the Science Translational Medicine review on 31 October 2012.

In France, nearly 200,000 individuals suffer from chronic inflammatory bowel disease, known as IBD, (specifically Crohn’s disease and ulcerative colitis). The occurrence rate of this type of disease continues to rise (8,000 new cases diagnosed per year). During inflammatory outbreaks, IBDS are chiefly characterised by abdominal pain, frequent diarrhoea (sometimes with bleeding) or even disorders in the anal area (fissure, abscesses). These symptoms mean that taboos are associated with these diseases.

Different avenues are being explored to explain the origin of IBDS, including the role of genetic or environmental factors. The intestinal flora seems to play an important role in the outbreak of inflammation, although little is known about it. Identifying an effective treatment is also at the heart of the investigations.

Researchers are focusing on a human protein, known for its anti-inflammatory properties: Elafin. Although this protein is found naturally in the intestine to protect it against attacks, it disappears in patients suffering from IBDS.

Their hypothesis? Administering Elafin directly into the intestine could protect against inflammatory attacks and restore intestinal equilibrium and its functions.

Using non-pathogenic bacteria found naturally in the intestine and food, scientists from Inserm and Inra have designed modified bacteria to produce Elafin. To this end, the human Elafin gene, isolated in collaboration with a team from the Institut Pasteau, was introduced in Lactococcus lactis and Lactobacillus casei, two food-grade bacteria found in dairy products.

Results in mice...

When administered orally to mice, the human Elafin-producing bacteria are found a few hours later on the surface of the intestine where they deliver the anti-inflammatory protein. In different mice models of chronic or acute intestinal inflammation, oral treatment using these Elafin-producing bacteria provided significant protection of the intestine and decreased inflammatory symptoms.

... and in humans

Elafin expressed by these bacteria also protects cultured human intestinal cell lines from inflammatory outbreaks similar to those observed in chronic inflammatory bowel diseases. Elafin produced in this way restores the equilibrium of intestinal mucus by reducing inflammation and accelerating cell healing processes.

Potential clinical applications

These results may result in a clinical application where Elafin would be administered to patients suffering from IBDS using beneficial bacteria (probiotic), which are already commonly found in food (yoghurt, cheese), thus protecting the patients from inflammatory symptoms. According to the researchers "This kind of secure treatment could even be used over the long-term, to treat inflammatory diseases."

This research is protected by a patent and an exclusive licence assigned to an industrial partner, managed by Inserm Transfert.

Sources

Food-grade bacteria expressing Elafin protect against inflammation and restore colon homeostasis.
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How bacteria talk to each other and our cells

Bacteria can talk to each other via molecules they themselves produce. The phenomenon is called quorum sensing, and is important when an infection propagates. Now, researchers at Linköping University in Sweden are showing how bacteria control processes in human cells the same way.

The results are being published in PLOS Pathogens with Elena Vikström, researcher in medical microbiology, as the main author.

When the announcement goes out, more and more bacteria gather at the site of the attack – a wound, for example. When there are enough of them, they start acting like multicellular organisms. They can form biofilms, dense structures with powers of resistance against both antibiotics and the body's immune defence system. At the same time, they become more aggressive and increase their mobility. All these changes are triggered when the communication molecules – short fatty acids with the designation AHL – fasten to receptors inside the bacterial cells; as a consequence various genes are turned on and off.

AHL can wander freely through the cell membrane, not just in bacterial cells but also our own cells, which can be influenced to change their functions. In low concentrations white blood cells, for example, can be more flexible and effective, but in high concentrations the opposite occurs, which weakens our immune defences and opens the door for progressive infections and inflammations.

A team at Linköping University is the first research group in the world to show how AHL can influence their host cells. Using biochemical methods, the researchers have identified a protein designated IQGAP, which they single out as the recipient of the bacteria's message, and something of a double agent.

“The protein can both listen in on the bacteria’s communication and change the functions in its host cells,” Vikström says.

Their laboratory studies were carried out on human epithelial cells from the intestines, which were mixed with AHL of the same type produced by Pseudomonas aeruginosa, a tough bacterium that causes illnesses in places like the lungs, intestines, and eyes. With the help of mass spectrometry, they have been able to see which proteins bind AHL.

“We have proof that physical contact between bacteria and epithelial cells is not always required; the influence can happen at a distance,” Vikström says.

The team’s discovery can open the door to new strategies for treatment where antibiotics cannot help. One possibility is designing molecules that bind to the receptor and block the signal path for the bacteria – something like putting a stick in a lock so the key won’t go in. It’s a strategy that could work with cystic fibrosis, for example, an illness where sticky mucus made of bacterial biofilm and large amounts of white blood cells is formed in the airways.


Exome Sequencing Project Has Some Surprising Results

ScienceDaily (Nov. 6, 2012) — A multi-institutional team of researchers has sequenced the DNA of 6,700 exomes, the portion of the genome that contains protein-coding genes, as part of the National Heart, Lung and Blood Institute (NHLBI)-funded Exome Sequencing Project, one of the largest medical sequencing studies ever undertaken.

Scientists participating in the project initially expected that individual rare variants would have a greater effect on over 80 heart, lung and blood related traits and diseases of high public health significance, said Suzanne M. Leal, Ph.D., professor and director, Center for Statistical Genetics in the Department of Molecular and Human Genetics of Baylor College of Medicine in Houston, TX.

The researchers found that many (1.1 million) of the 1.2 million coding variants that they identified in exome data from 4,420 European-Americans and 2,312 African-Americans occurred very infrequently in the population and often were only observed in a single individual, explained Dr. Leal, who presented the findings November 6 at the American Society of Human Genetics 2012 meeting.

Dr. Leal added that most of the observed coding variants are population specific, occurring in either European or African Americans. “Of the identified variants, about 720,000 change the genetic code in a manner that could produce flawed proteins. Yet the role played by most of these variants in disease development has not been established,” she said.

The major goal of the project was to understand how variation in the exome affects heart, lung and blood related traits and diseases.
The study participants were selected from a sample of over 220,000 individuals who participated in another National Institute of Health (NIH) supported study that had collected extensive medical data on the participants. "Individuals were selected to have a disease endpoint of interest or an extreme trait value of public health importance," said Dr. Leal.

By sequencing the exomes of 91 cystic fibrosis patients, Dr. Leal and her research colleagues discovered and replicated an association between variants in the DCTN4 gene and when a patient first develops a Pseudomonas aeruginosa airway infection.

The researchers were also able to replicate many known associations between individual DNA variants and traits, such as high blood levels of low-density lipoprotein, known as the 'bad' cholesterol, and C-reactive protein, which increases the body's response to inflammation.

The majority of these findings are for variants that are common in the population, said Dr. Leal.

To detect associations with rare variants, analyses were performed by aggregating information from individual variants within a gene. This approach successfully detected an association with rare variants in the APOC3 gene that lowers triglyceride levels, an unhealthy type of fat in the blood, said Dr. Leal.

"In order to detect associations with rare variants, due to their modest effects, very large samples sizes are required. In many cases the data from the Exome Sequencing Project gave us leads that had to be evaluated using more study subjects. One mechanism for doing this was by genotyping additional samples using the exome chip, which contains approximately 240,000 coding variants. The Exome Sequencing Project played a very important role in the development of the exome chip, by being the largest contributor of data," she added.

According to the NHLBI, exome sequencing is an efficient way to search for rare variants associated with complex traits. In contrast to previous genome wide association studies (GWAS), which concentrated on common variants scattered throughout the genome, exome sequencing has the potential to accelerate the search for unambiguous genetic links to disease by focusing attention on the protein coding portion of the genome.

In the journal Science, Dr. Leal and her colleagues wrote that GWAS have substantially improved knowledge about common genetic variation, but have been generally uninformative about the patterns of rare variation within the protein coding regions of the genome.

"This is a very new field for which new methodology had to be developed. We learned many lessons in the quality control and analysis of exome data, as well as what types of results one would expect to see when analyzing rare variants. Additionally, the Exome Sequencing Project has been extremely valuable in obtaining a better understanding of population genomics and the history of man," Dr. Leal said.

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**Novel Process Represents Faster and More Economical Route for Devising Countermeasures Against Biothreats, Scientists Say**

ScienceDaily (Nov. 5, 2012) — Texas Biomedical Research Institute scientists have developed a faster, less expensive route to screen suitable tests for bioterror threats and accelerate the application of countermeasures.

The new process screens for pairs of affinity reagents—molecular magnets that bind to and hold on to their targets, be they toxins, viruses or bacteria. That will enable countermeasures to be selected and utilized much faster than the current practice. "Using crude extracts from *E. coli*, the workhorse bacterium of the biotechnology laboratory, the new route bypasses the need for purification and complex equipment, enabling screening to be performed in under an hour," said Andrew Hayhurst, Ph.D., a Texas Biomed virologist in San Antonio, Texas.

Normally, he said, such screening requires sophisticated costly equipment to purify and analyze the affinity reagents. Such analysis becomes a huge burden when hundreds of reagents need to be checked and can take weeks to months.
The process—funded primarily by Texas Biomed and the San Antonio Area Foundation, and in part by the Defense Threat Reduction Agency and the National Institutes of Health (NIH)—was described online in the November 5, 2012 issue of Nature Publishing Group’s Scientific Reports.

"We need an inexpensive route to screen libraries of affinity reagents. It had to be simple and self-contained as we eventually needed it to work in the space-suit lab or hot zone," said Hayhurst.

His surprisingly simple scheme allows scientists to make stop-gap tests to any given biological threat in a matter of days, with the screening step completed in an hour. The goal now is to speed up the entire process to work within a single day.

Hayhurst initially developed the pipeline using llama antibodies as the affinity reagents to botulinum neurotoxins, known as the world’s most poisonous poisons—100 billion times more toxic than cyanide and handled in a specialized biosafety cabinet at biosafety level 2. Satisfied that the system was working, he then took it into the biosafety level 4 laboratory with his assistant, Laura Jo Sherwood, and they generated a stop-gap test for Ebolavirus Zaire in days. This virus has been shown to be 95 percent lethal in outbreak settings and with no vaccine or therapeutic it is a risk to the U.S. through importation.

Botulinum neurotoxins and Ebolavirus are among a handful of threats now categorized as Tier 1 agents, presenting the greatest risk of deliberate misuse with the most significant potential for mass casualties or devastating effects to the economy, critical infrastructure; or public confidence.

"Being able to respond quickly to known biological threats will better prepare us for combating emerging and engineered threats of the future," Hayhurst said. "However, the great thing about this test pipeline is that it can be applied to almost any target of interest, including markers of diseases like cancer."

The Evolution of Creationism
ScienceDaily (Nov. 2, 2012) — Throughout history, people have sought to understand how the world came to be and how it has changed over time. This curiosity has produced a rich legacy of science and philosophy and impacted and influenced religion and theology. In the November 2012 issue of GSA Today, David Montgomery of the University of Washington examines both the history of geology and of biblical views regarding Earth’s origins.

Montgomery’s main premise is that throughout most of the past several hundred years, scientists and theologians engaged in extensive collaboration regarding issues like Earth’s age and origin. The common bond that sustained this rich exchange of ideas was a respect for reason and a trust in the scientific process.

As modern science evolved, so did many shared questions and struggles regarding how to best understand Earth’s age as well as how new scientific findings harmonized with or conflicted with theological understanding as conveyed in works such as the Bible. These questions and struggles persist into the present, most notably in geology, where vast differences in the answers to such fundamental questions as "how old is this planet?" both correlate and contrast with some religious beliefs.

In terms of Christian theology, the main problems that Montgomery discusses are Earth’s age and the role of a global flood ("Noah’s flood") in geological history. While these issues—that Earth is not over four billion years old, but is actually only a few thousand years old, and that most of the geological history recorded by rocks was formed as a result of Noah's flood—are commonly raised by modern-day creationists, they have also been vigorously studied by both scientists and theologians over the past several hundred years.

Montgomery shows that geologists have provided a vast array of evidence that refutes both a young age for Earth and a worldwide flood. These conclusions provoked significant debate among Christian writers during the early 1800s, but many acknowledged the validity of the scientific evidence. They subsequently adapted their view of creation as spelled out in the Bible, recognizing that it might be figurative instead of literal, and that Noah’s flood was likely a regional event that involved the Caspian or Black Sea.

Modern-day creationism, according to Montgomery, developed from several influential efforts, beginning in the 1920s. The movement would revive the global (Noah’s) flood explanation for the geological record, resurrecting the older theory mainly in an effort to question scientific conclusions regarding the biological evolution of life on Earth.

The creationists of the twentieth century—and those of today—evolved in order to reject a scientific basis for understanding of the history of our planet. They instead rely on a literal interpretation of Biblical accounts of creation.
These arguments are effective. Montgomery points out more than 40% of Americans believe Earth is less than 10,000 years old, despite overwhelming scientific evidence to the contrary. However, Montgomery hopes that by pointing to our longer-term history and mutual heritage of using scientific observations of the natural world to inform both secular and religious understanding, the relationship between science and religion can undergo further evolution, and faith in science can be restored.

Journal Reference:

Growing Number Of Dengue Cases In India Increases Risk Of Disease Spreading Worldwide, Experts Warn

"An epidemic of dengue fever in India is fostering a growing sense of alarm even as government officials here have publicly refused to acknowledge the scope of a problem that experts say is threatening hundreds of millions of people, not just in India but around the world," the New York Times reports. Dengue is endemic in half of the world's countries and continuing to spread, experts say, according to the newspaper. In India's capital, New Delhi, "where areas of standing water contribute to the epidemic's growth, hospitals are overrun and feverish patients are sharing beds and languishing in hallways," the newspaper writes. With officials citing 30,002 cases of dengue in India through October, "a 59 percent jump from the 18,860 recorded for all of 2011," several experts say the true number of infections in the country is in the tens of millions, the New York Times notes.

"A central piece of evidence for those who contend that India suffers hundreds of times more dengue cases than the government acknowledges is a recent and as yet unpublished study [pdf] of dengue infections in West Bengal that found about the same presence of dengue as in Thailand, where almost every child is infected by dengue at least once before adulthood," the New York Times writes. Most cases of dengue result in mild fever and fatigue or more serious flu-like symptoms, but "[i]n about one percent of cases, dengue advances to a life-threatening cascade of immune responses known as hemorrhagic or shock dengue," the newspaper notes, adding, "The great danger of having hundreds of millions of people in India with undiagnosed and unacknowledged primary infections is that a sudden shift in the circulating dengue strain could cause a widespread increase in life-threatening illnesses" (Harris/Kumar, 11/6). A separate article in the New York Times' "India Ink" blog describes the type of mosquito that carries dengue and challenges to reducing the disease's spread (Harris, 11/7).

International Community Must Continue To Support Cholera Treatment, Prevention In Haiti

Since its arrival in Haiti two years ago, "cholera has sickened more than 600,000 people and killed more than 7,500," and "[t]his year the epidemic is on track to be among the world's worst again, with nearly 77,000 cases and 550 deaths, according to the Haitian Ministry of Health," Ralph Ternier and Cate Oswald of Zanmi Lasante/Partners in Health in Haiti write in the Huffington Post's "Impact" blog.
"Despite the decrease in cases from 2011, every new case represents an unnecessary and preventable infection and an even further potential of completely preventable and unnecessary death in hardest-to-reach areas," they state. Though a "multi-pronged approach" to treating and preventing cholera has significantly decreased the number of cases, "[t]he sad reality is that ... we know that cholera is not going away, [yet] emergency funding for cholera is," they write.

"If we continue treating cases at the rate we are now, our dedicated cholera funding will be gone in a few short months, and we have no new funds on the horizon," Ternier and Oswald write, adding, "And we're one of a shrinking number of medical organizations partnering with the Haitian Ministry of Health to continue to provide prevention and treatment for cholera." They continue, "We'll be blunt: The loss of funding means that in months, thousands of patients—people we have the tools, skills, and expertise to save—will become sick, and hundreds more may needlessly die. This wouldn't be accepted in a wealthy country. And we're not willing to accept it in Haiti." Ternier and Oswald conclude, "We need the ongoing support of the international community, now more than ever, to help us advocate for continued investments in water and sanitation infrastructure and for more accessible high quality health care options, especially for the rural poor" (11/6).
When parasites catch viruses
Researchers find a viral symbiont of a protozoan parasite increases virulence to the human host

When humans have parasites, the organisms live in our bodies, co-opt our resources and cause disease. However, it turns out that parasites themselves can have their own co-habitants.

Researchers from Harvard Medical School, Brigham and Women's Hospital and SUNY Upstate Medical University have found that the pathogenicity of the sexually transmitted protozoan parasite *Trichomonas vaginalis*—the cause of trichomoniasis—is fueled by a viral invader. Trichomoniasis infections are more common than all bacterial STDs combined. Annually, trichomoniasis affects nearly 250 million people, typically as vaginitis in women and urethritis in men.

"Trichomoniasis is associated with devastating consequences for women due to inflammation and related risks of reproductive disease," said Raina Fichorova, leader of the research team as well as associate professor of obstetrics, gynecology and reproductive biology at Brigham and Women's Hospital. "Our future goal is to determine how the viral symbiont and its inflammatory 'halo' affect the risk of preterm delivery and low birth weight."

"This is only one of two incidences that we know of for which the pathogenicity of a protozoan virus has been characterized," said Max Nibert, Harvard Medical School professor of microbiology and immunology and co-author of the paper. "When found together, the result is an increase in virulence of the protozoan parasite to the human host, leading to exacerbated disease."

This study, which was initiated by a Harvard Catalyst Pilot grant, will be published online in *Public Library of Science (PLOS)* One.

Rather than invading human cells, *Trichomonas vaginalis* attaches to their surface and feeds on them, sometimes remaining asymptomatic for a period of time. The virus, called *Trichomonasvirus*, infects the protozoan and increases its pathogenic power by fueling virus-specific inflammatory responses.

Moreover, carrying the protozoan parasite predisposes women to acquire sexually transmitted viruses, particularly HIV and human papillomavirus, or HPV, both of which can lead to serious diseases such as AIDS and cervical cancer, respectively. Fichorova and Nibert have recently obtained funding from the Harvard University Center for AIDS Research to find out if the virus itself is directly responsible for increased HIV risk.

According to Nibert, the virus-parasite symbiosis is the norm rather than the exception with this particular protozoan. Upwards of 80 percent of *Trichomonas vaginalis* isolates carry the virus. "Unlike flu viruses, for example, this virus can't spread by jumping out of the cell into another one," said Nibert, who has pioneered molecular biology work on double-stranded RNA viruses, a category that includes *Trichomonasvirus*. "It just spreads between cells when they divide or mate."

According to the researchers, it is this double-stranded nature of the viral genome that contributes to increased virulence of the protozoan parasite. "The double-stranded RNA seems important to the signaling process," added Nibert.

Currently, trichomoniasis is treated with the antibiotic metronidazole. But this treatment is only effective on the protozoan. "When the medication is used, the dying or stressed protozoa release unharmed virions, which then signal to the human cells," explained Fichorova. As a result, the symptoms are aggravated, and this in turn might increase the danger it poses to pregnant women and their children.

"Ahead is more research to better understand the viral cycle and structural features that might be vulnerable to drugs, which will lead to opening new doors for better treatment of trichomoniasis and related diseases," said Fichorova. "Our complementary expertise, interdisciplinary team efforts and strong collaboration is the key to our future success."

Nibert added that basic research on *Trichomonas vaginalis* is not nearly as supported as he thinks it should be. "It is unfortunate that a human pathogen of such worldwide significance has been neglected to such a degree," he said.

Cell damage caused by personal lubricants does not increase HIV risk

PITTSBURGH, Nov. 7, 2012 – The use of certain water-based, over-the-counter personal lubricants can dry out and irritate vaginal and rectal tissue, but does not appear to increase susceptibility to HIV, according to a laboratory study published today in *PLoS ONE*. Even so, say study authors affiliated with the National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN), more research is needed to fully understand the safety of personal lubricants and their effect on epithelial tissue, the layer of mucosal cells that acts as the body's first line of defense against sexually transmitted HIV.
"We tested several kinds of personal lubricants and those that did the most damage to cell tissue were hyperosmolar," said lead study author Charlene S. Dezzutti, Ph.D., associate professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine and principal investigator of the MTN Network Laboratory.

"While we know there is cellular toxicity associated with hyperosmolar lubes, the damage did not appear to make cells more vulnerable to HIV infection," Dr. Dezzutti explained.

Hyperosmolar lubricants contain more salts, carbohydrates and proteins than are typically found inside cells of the vagina or rectum. This imbalance causes epithelial cells to lose water and, as a result, dry out. They are different from iso-osmolar lubricants, which contain the same amount of salts and other ingredients as do the cells.

Study investigators tested 14 brand-name over-the-counter and mail-order water-, lipid- and silicon-based lubricants. Lubricants selected were identified as those most commonly used during anal sex in a survey of more than 6,300 respondents. Results indicated that hyperosmolar water-based lubricants caused the most damage to the epithelium in the vagina and rectum compared to iso-osmolar water- and silicon-based lubricants. When the researchers applied the lubricants to vaginal tissue and then exposed it to HIV, they found that the lubricants did not increase susceptibility to HIV. Other studies are seeking to address HIV susceptibility with rectal tissue.

Of the lubricants tested, Good Clean Love and PRÉ, both water-based iso-osmolar lubricants, were shown to be least harmful to epithelial tissue, along with two silicon-based lubricants, Female Condom 2 and Wet Platinum. Lubricants that were most toxic to the epithelial tissue (Gynol II, KY Jelly and Replens) also tended to damage "good" bacteria called lactobacillus, which is needed to maintain a healthy genital tract.

"Much more work needs to be done to explore the safety of lubes," said Dr. Dezzutti. "This was an early study and the jury is still out as to whether hyperosmolar lubes cause damage to the epithelium that in conjunction with other processes, like inflammation, could increase susceptibility to HIV."

"The most important point for people to take away from this study is that condoms are still the best way to protect against HIV and that lubes should always be used with compatible condoms."

**Humans, Chimpanzees and Monkeys Share DNA but Not Gene Regulatory Mechanisms**

ScienceDaily (Nov. 6, 2012) — Humans share over 90% of their DNA with their primate cousins. The expression or activity patterns of genes differ across species in ways that help explain each species' distinct biology and behavior.

DNA factors that contribute to the differences were described on Nov. 6 at the American Society of Human Genetics 2012 meeting in a presentation by Yoav Gilad, Ph.D., associate professor of human genetics at the University of Chicago.

Dr. Gilad reported that up to 40% of the differences in the expression or activity patterns of genes between humans, chimpanzees and rhesus monkeys can be explained by regulatory mechanisms that determine whether and how a gene's recipe for a protein is transcribed to the RNA molecule that carries the recipe instructions to the sites in cells where proteins are manufactured.

In addition to improving scientific understanding of the uniqueness of humans, studies such as the investigation conducted by Dr. Gilad and colleagues could have relevance to human health and disease.

"Through inter-species' comparisons at the DNA sequence and expression levels, we hope to identify the genetic basis of human specific traits and in particular the genetic variations underlying the higher susceptibility to certain diseases such as malaria and cancer in humans than in non-human primates," said Dr. Gilad.

Dr. Gilad and his colleagues studied gene expression in lymphoblastoid cell lines, laboratory cultures of immortalized white blood cells, from eight humans, eight chimpanzees and eight rhesus monkeys.

They found that the distinct gene expression patterns of the three species can be explained by corresponding changes in genetic and epigenetic regulatory mechanisms that determine when and how a gene's DNA code is transcribed to a messenger RNA (mRNA) molecule.

Dr. Gilad also determined that the epigenetics process known as histone modification also differs in the three species. The presence of histone marks during gene transcription indicates that the process is being prevented or modified.
"These data allowed us to identify both conserved and species-specific enhancer and repressor regulatory elements, as well as characterize similarities and differences across species in transcription factor binding to these regulatory elements," Dr. Gilad said.

Among the similarities among the three species were the promoter regions of DNA that initiated transcription of a particular gene.

In all three species, Dr. Gilad's lab found that transcription factor binding and histone modifications were identical in over 67% of regulatory elements in DNA segments that are regarded as promoter regions.

The researchers presentation is titled, "Genome-wide comparison of genetic and epigenetic regulatory mechanisms in primates."

**Vaccine to Help Prevent Deadly Hendra Virus**

ScienceDaily (Nov. 5, 2012) — A scientific discovery made in the laboratory of Christopher C. Broder, Ph.D., professor of microbiology and immunology at the Uniformed Services University of the Health Sciences (USU), has led to the development of a vaccine to aid in the prevention of the deadly Hendra virus. On Nov. 1, Pfizer Animal Health announced that the new vaccine, called Equivac® HeV, is now available for use in Australia.

Since its first appearance in 1994, the Hendra virus has killed more than 80 horses and four of the seven people infected to date. An equine vaccine is crucial to breaking the cycle of Hendra virus transmission from flying foxes to horses and then to people, as it helps to prevent the horse from both developing the disease and transmitting the virus to other horses and people. Experiments have shown that vaccinated horses survived infection by Hendra virus and have shown no evidence of virus, disease, replication or shedding of the virus, a critical finding to help prevent transmission.

The vaccine is derived from original work by Broder and Katharine Bossart, Ph.D., a USU alumna and assistant professor at Boston University School of Medicine. Their work was supported by the National Institute of Allergy and Infectious Disease (NIAID), part of the National Institutes of Health.

"The vaccine component is a soluble portion of a Hendra virus G glycoprotein, known as Hendra-sG," said Broder. Bossart developed Hendra-sG while a graduate student in Broder's laboratory at USU. "This glycoprotein is critical in mediating viral infection. If you block its function, you block virus infection. We have shown it to be highly effective in preventing Hendra virus and the related Nipah virus infection when it is used as a vaccine in animals. Vaccinated animals make antibodies to Hendra G, and these antibodies will subsequently prevent virus infection."

To date, Hendra virus has been found only in Australia. The nation experienced an unprecedented number of 18 outbreaks across Queensland and New South Wales in 2011, during which 22 horses died or were euthanized. Authorities detected the first case of Hendra virus antibodies in a dog within a natural environment that same year. The virus has appeared seven times in 2012, causing equine deaths and serious cases of human exposure to infection. In July 2012, a woman with significant exposure risk was given an experimental human monoclonal antibody therapy on a compassionate use basis. Dimitar Dimitrov, Ph.D., of the NIH, working in collaboration with Broder, developed the antibody, known as m102.4.

The Hendra virus, and the similar Nipah virus, both members of the paramyxovirus family, are highly infectious agents that emerged from flying foxes in the 1990s to cause serious disease outbreaks in humans and livestock in Australia, Bangladesh, India, Malaysia and Singapore. Recent Nipah outbreaks have resulted in acute respiratory distress syndrome and encephalitis, person-to-person transmission, and greater than 75 percent case fatality rates among humans. A collaborative group led by Broder published its groundbreaking Hendra and Nipah virus work in two articles in *Science Translational Medicine*, including the Aug. 2011 article that describes the Hendra–sG vaccine’s ability to completely protect nonhuman primates from Nipah virus infection, paving the way for a potential human-use vaccine, and the Oct. 2011 article that describes a breakthrough in the development of an effective therapy against both viruses now in development for use in humans.

Broder and Bossart collaborated with a team at the Commonwealth Scientific and Industrial Research Organisation’s (CSIRO) Australian Animal Health Laboratory (AAHL) in Geelong, Australia, to advance the Hendra vaccine technology. The bio-security facility at AAHL is the only laboratory in the world where Hendra virus challenge testing of the vaccine in horses could have been accomplished – work presently under the direction of Deborah Middleton, D.V.P. The technology used to develop the vaccine was licensed from The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF) by Pfizer Animal Health, who joined the collaborative effort two years ago, bringing its development and
regulatory expertise to facilitate the unprecedented rapid development, approval and deployment of the breakthrough vaccine.

**Very high HIV incidence among men who have sex with men in Kenya**

Michael Carter
Published: 07 November 2012

HIV incidence among men who have sex with men (MSM) in Kenya is as high as 35%, investigators report in the online edition of *AIDS*. Incidence was just 6% for bisexual men, but was 35% in men who only had sex with other men.

The study adds to the growing body of evidence showing the severity of the HIV epidemic among MSM in Africa.

“MSME [men who reported sex exclusively with men], who have been referred to as ‘queens’ in Kenya, experience very strong societal rejection and may face greater barriers than MSMW [men who reported sex with men and women] to accessing medical services,” comment the authors.

Group sex and recent infection with gonorrhoea were among the risk factors for acquisition of HIV.

Results also showed that men infected with HIV maintained viral loads associated with a high risk of HIV transmission for around three-quarters of the time during the two years after seroconversion, despite the fact that the majority were not eligible for antiretroviral treatment owing to having CD4 cell counts above 350 cells/mm³.

Same-sex behaviour is criminalised in Kenya and is also highly stigmatised. This is also the case in many other African settings. Recent research has shown that HIV prevalence among MSM equals or exceeds that seen in the general population in most sub-Saharan countries.

Investigators in Kenya wanted to establish a clearer understanding of the rate of new HIV infections among MSM. The researchers also wanted to see if HIV incidence differed between bisexual men and men who reported sex exclusively with other men. They also analysed the risk factors for infection with HIV and monitored the viral load of individuals who seroconverted for two years after their diagnosis.

Recruitment to the prospective study started in 2005. MSM were recruited via walk-in clinics in the coastal towns of Mtwapa and Kilifi, or via personal contacts.

Participants were tested for HIV and other sexually transmitted infections (STIs) when they were recruited to the study. At this time, they also had face-to-face interviews with clinic staff about their sexual behaviour. Follow-up was every three months.

A total of 449 HIV-negative MSM were recruited to the study. Of these, 372 (83%) reported sex with men and women. The remaining 77 men (17%) reported sex exclusively with other men.

Bisexual men were more likely to report insertive anal sex; exclusively homosexual men were more likely to report receptive anal sex (p < 0.001).

Overall, the men contributed 744 person-years of follow-up. The median duration of follow-up was 21 months for bisexual men, compared to 5 months for exclusively homosexual men (p 0.001).

In all, 64 men (9%) were infected with HIV. Incidence was 6% for bisexual men compared to 35% for men who exclusively had sex with other men (p < 0.001).

Factors associated with infection with HIV included: exclusive homosexual behaviour (aIRR = 3.7; 95% CI, 2.1-6.5); recent unprotected sex (aIRR = 2.1; 95% CI, 1.1-4.1); group sex (aIRR = 1.99; 95% CI, 1.0-3.4); and recent infection with gonorrhoea (aIRR = 14.7; 95% CI, 8.3-26.0).

Monitoring of viral load in the men who became infected with HIV showed that 75% of measurements were over 10,000 copies/ml in the two years after seroconversion. CD4 cell counts fell below 350 cells/mm³ on only 13% of study visits, indicating that the vast majority of infected men would not have qualified for antiretroviral therapy.

“The very high HIV-1 incidence among MSM from Coastal Kenya may be the result of studying interconnected networks of adults with ongoing high-risk sexual activity,” comment the investigators.

“Interventions aiming to reduce HIV-1 acquisition and transmission among MSM in Kenya should include frequent, targeted HIV testing and linkage to care, with a strong focus on effective biomedical interventions such as pre-exposure prophylaxis (PrEP) and early ART.”

**Reference**

Does Muslim religion have an impact on HIV transmission?
7 Nov, 12 | by Leslie Goode, Blogmaster

How is it that the nations of the Middle East and North Africa appear to have relatively low rates of HIV (see [http://blogs.bmj.com/sti/2011/09/19/bringing-to-light-the-hiv-epidemiology-of-%E2%80%9Chidden%E2%80%9D-msm-populations-in-the-middle-east/](http://blogs.bmj.com/sti/2011/09/19/bringing-to-light-the-hiv-epidemiology-of-%E2%80%9Chidden%E2%80%9D-msm-populations-in-the-middle-east/))? A recent paper in the American Sociological Review – Adamczyk & Hayes – seeks to demonstrate that the predominance of the Muslim religion in a country may have a macro-level, cultural impact on the sexual behaviour (pre- and extra-marital sex) of its residents. What do they mean by qualifying religious impact as, to some extent, macro-level and cultural? They are claiming that the impact of religion is not reducible either to individual affiliation, or to formal restrictions. In their words, it is, in their words sui generis – unique of its kind. Behind this is a Durkheimian understanding of the religious group as something more than the sum of its parts ([http://asr.sagepub.com.libproxy.ucl.ac.uk/content/77/5/723.abstract](http://asr.sagepub.com.libproxy.ucl.ac.uk/content/77/5/723.abstract)).

To test their hypothesis the authors use data from the Demographic and Health Survey (DHS). Their most interesting findings relate to pre-marital sex. Muslims are far less likely to report pre-marital sex than Christians/Jews (0.61: 0.77). This effect is not explained wholly by age of first marriage. As the proportion of Muslims in a nation increases likelihood of all residents (including non-Muslims) reporting pre-marital sex decreases substantially. So, for a non-working rural woman, likelihood of premarital sex is 0.71 where 1% residents are Muslim, 0.61 where 23% are Muslim, 0.28 where 90% are Muslim. Muslims, however, are not more likely to report pre-marital sex as the proportion of Muslims decreases. Interestingly the relationship between likelihood of pre-marital sex and percentage Muslim does not seem to be mediated by formal restrictions (exemplified here by restrictions on women’s mobility).

The tentative conclusion of the study is, therefore, that the striking relationship of pre-marital sex and percentage Muslim may not be a matter of individual affiliation (or Muslims would be more likely to report pre-marital sex where percentage Muslim decreases). It may also not be a matter of formal restriction, for in that case the relationship of pre-marital sex to percentage Muslim would be mediated by women’s mobility). Hence the relationship is likely to be explained by something other than individual affiliation, nor formal restriction – i.e. probably macro-level cultural effect.

To non-sociologists this argument from premises to conclusion might seem tenuous. However hypothesis of a relationship between religion and behaviour is interesting, and the authors claim that this is the first serious attempt to test such a hypothesis on the basis of international data. The interest of the paper for STI journal readers may go beyond the intriguing question of why certain populations should be less susceptible to HIV epidemics than others. From the angle of sexual health policy, the claims of Adamczyk & Hayes matter because they suggest the existence of other potentially refractory cultural factors (i.e. religion in the sense of Adamczyk & Hayes) – a “black box”, if you like – that, depending on the policy, could turn out to have negative as well as positive effects. On the face of it, this seems at least plausible, and, if the case, would certainly be important for health policy. To the extent it militates against “one-size-fits-all” approaches to health policy, the argument of Adamczyk & Hayes may be additional ammunition in the “armamentarium” of the “programme science” based approach that is a topic of ongoing comment in this journal (see for example Aral & Blanchard: [http://sti.bmj.com/content/88/3/157.abstract?sid=a6ddd8144-b34c-4bcd-a4b2-0f997ae60fdo](http://sti.bmj.com/content/88/3/157.abstract?sid=a6ddd8144-b34c-4bcd-a4b2-0f997ae60fdo)). STI journal readers will be interested to know that STI journal continues to run a series on Programme Science, edited by Dr Sevgi Aral.

Significant relationship between mortality and telomere length discovered

A team of researchers at Kaiser Permanente and the University of California, San Francisco (UCSF) has identified a significant relationship between mortality and the length of telomeres, the stretches of DNA that protect the ends of chromosomes, according to a presentation on Nov. 8 at the American Society of Human Genetics 2012 meeting in San Francisco.

While a reduction in telomere length is regarded as a biomarker of aging, scientists have not yet determined whether it plays a direct causal role in aging-related health changes and mortality or is just a sign of aging.

In their prospective study of 100,000 multi-ethnic individuals whose average age was 63 years, the researchers determined that an association between telomere length and mortality existed and persisted even after the data were adjusted for such demographic and behavioral factors as education, smoking and alcohol consumption, said Catherine Schaef er, Ph.D., director of the Kaiser Permanente (KP) Research Program on Genes, Environment and Health (RPGEH).
Dr. Schaefer and Neil Risch, Ph.D., director of the UCSF Institute for Human Genetics, are principal investigators of the Genetic Epidemiology Research Study on Adult Health and Aging (GERA). UCSF professor and Nobel laureate Elizabeth Blackburn, Ph.D., led the research on telomere length measurement.

The telomere research, part of the GERA project, has genotyped over 675,000 markers of 100,000 KP Northern California patients and linked them with health data from their electronic medical records. To obtain DNA for genotyping and telomere measurement, the researchers collected saliva samples from the patients, who volunteered for the project and provided scientists with access to their electronic medical records.

Two years prior to the saliva collection, the researchers conducted a detailed survey of the patients' demographic and behavioral factors, providing a unique opportunity to address questions of telomere epidemiology and aging.

"With these data, we examined demographic relationships with telomere length, behavioral influences and relationship of telomere length with all causes of mortality following sample collection," said Dr. Schaefer. "Although we found that shorter-than-average telomeres were prospectively associated with mortality, only those with the shortest telomeres were at increased risk of death."

Dr. Risch added, "While this could indicate a direct effect of telomere length on health, it will also be important to examine the extent of pre-existing diseases in these individuals to understand their possible role in the biological connection between telomere length and longevity."

Dr. Risch said that he and the other scientists expected to and did find that telomere length was inversely correlated with age, and women had longer telomeres than men except as young adults. All analyses controlled for age and gender.

Harvard Medical School scientist Cynthia C. Morton, Ph.D., who was not involved in the study, commented, "The GERA study is especially impressive for the large resource of DNA samples and corresponding electronic medical records available from KP patients, and for the outstanding group of scientists collaborating in the research.

"The intriguing findings on telomere length in the GERA cohort are no doubt among many yet forthcoming, prompting further investigations into the basis for ethnic differences in telomere length such as whether specific oral environmental exposures in ethnic groups might account for differences in telomere lengths in saliva DNA samples," added Dr. Morton, William Lambert Richardson Professor in Harvard's department of obstetrics, gynecology and reproductive biology.

Like several other investigations, GERA detected significantly longer telomeres among African Americans than other groups, but did not reveal a significant difference between European-Americans, Latinos and Asians.

According to the GERA results, telomere length was positively correlated with such factors as level of education and body mass index (BMI), and negatively correlated with cigarette smoking and alcohol consumption. However, telomere length was not associated with major depression or stress-related disorders, although other studies have reported an association between telomere length and depression and stressful events.

Links between shorter telomeres and risks for cardiovascular disease, diabetes, some cancers, depression, pulmonary fibrosis, vascular dementia, osteoarthritis and osteoporosis have been detected by Dr. Blackburn, one of three scientists honored with the 2009 Nobel Prize in Physiology or Medicine, and her research group as well as other labs. Telomeres are special DNA sequences attached to the ends of each of the 46 chromosomes in human cells. When telomeres become too short, cells can no longer multiply.

Structural and Functional Insights into the HIV-1 Maturation Inhibitor Binding Pocket

Maturation of HIV-1 particles, which occurs as they bud off from the infected cell, is triggered by the step-wise cleavage of the major viral structural polyprotein, Pr55Gag, to individual, mature Gag proteins. The viral protease is the enzyme responsible for Gag polyprotein cleavage. Maturation inhibitors prevent the viral protease from processing Gag at one particular cleavage site, but how they accomplish this is not understood. In this study, the ability of HIV-1 to become resistant to the two structurally distinct maturation inhibitors that have thus far been reported was examined. We found that one of these compounds, PF-46396, gives rise to resistance mutations that map to three domains in Gag, including a region known as the major homology region (MHR). The MHR is highly conserved among retroviruses
and is known to be very important for virus assembly and maturation. These MHR mutants were observed to replicate much better in the presence of PF-46396 than in its absence; i.e., these mutants are compound-dependent. We were also able to select for second-site mutations in Gag that reversed the replication defects imposed by the MHR mutations. These results define residues in Gag that comprise the maturation inhibitor-binding pocket and also identify regions of Gag that structurally and functionally interact with the MHR.

**FDA: Fertility Doctor Didn’t Test Donors for STDs**


The US Food and Drug Administration (FDA) has sent a warning letter to Dr. Martin Balin, a Chicago fertility doctor, citing his clinic’s failure to meet standards for screening egg donors for STDs. On November 6, the FDA posted the letter to Dr. Balin on their website. FDA spokesperson Lisa Misevicz noted that nobody got sick, but the FDA’s goal is to “prevent anyone from becoming sick in the future.” The FDA wrote the letter after inspecting Balin’s Chicago office during June 20 through Aug. 17, 2012. During that time, an investigator found “significant deviations” from required screenings for egg donors.

The FDA inspects clinics that handle human tissue, including donated eggs, which can be used in assisting infertile couples to conceive. Females are usually paid to provide the eggs, which are retrieved and fertilized. The subsequent embryos are implanted in a recipient’s uterus. The FDA letter noted that Dr. Balin’s office did not meet the screening standards for gonorrhea, chlamydia, and HIV.

Balin told the Associated Press on November 7 that he has addressed the FDA’s concerns. He stated, “I think the testing was not clearly the way they wanted it.” Balin declared that the women receiving the donated eggs were safe because they took required preventive antibiotics. “Patients were always safe, that I can tell you,” explained Balin. He added that a lab that ran the wrong HIV test used another test instead.

Sean Tipton, spokesman for the American Society for Reproductive Medicine, noted that it is imperative to screen egg donors and that his organization’s standards are the same as those of the FDA. David Ball, president of the Society for Assisted Reproductive Technology and lab director of Seattle Reproductive Medicine, declared that, “There’s never been a reported case of any kind of disease transmission from egg donation. He added that screening is “a federal mandate, so we have to follow it.”

**Sexual Risk Behavior Among Youth with Perinatal HIV Infection in the United States: Predictors and Implications for Intervention Development**


A study by Katherine Tassiopoulos, of the Harvard School of Public Health, and colleagues examined sexual behavior of children born with HIV infection and who are now at the age of being sexually active. The researchers conducted cross-sectional and longitudinal analyses of youth aged 10–18 years who are enrolled in the US-based Pediatric HIV/AIDS Cohort Study between 2007 and 2009.

Of 330 youth, 92 (28 percent) reported having sexual intercourse, and 57 (62 percent) of the sexually active youth reported having unprotected sex. Only 33 percent disclosed their HIV status to their first partner. Youth living with a relative other than the biological mother had higher odds of engaging in unprotected sex than those living with a nonrelative. Of the 92 youth who were sexually active, 39 had a high viral load (greater than or equal to 5,000 copies/ml) after sexual initiation. Additional testing for 37 of the 39 youth indicated drug resistance.

The researchers concluded that as youth born with HIV become sexually active, certain behaviors can place their sexual partners at risk of acquiring HIV infection—and even drug-resistant HIV. The researchers recommend interventions for such teens including a focus on condom use, disclosure, treatment adherence, and safe sex practices to prevent further transmission of HIV/AIDS.

**How infection can trigger autoimmune disease**

Australian scientists have confirmed a ‘weak link’ in the immune system – identifying the exact conditions under which an infection can trigger an autoantibody response, a process not clearly understood until now.

We have known for many years that autoimmune diseases such as rheumatic fever and Guillain-Barré syndrome (where the body makes antibodies that attack the heart and peripheral nerves respectively) can occur after the body makes immune responses against certain infectious micro-organisms.
We have not been able to explain exactly how such examples of infection-driven autoimmunity occur, however, nor why our bodies seem unable to prevent them.

Our immune cells, such as the antibody-creating B cells, go through processes when they are first formed that ensure they are able to identify our own bodies, and therefore avoid self-attack. These processes are generally reliable as they take place in a steady, regulated way.

B cells go through a second and much more chaotic phase of development, however, when the body is fending off disease or infection. In order to cope with the immeasurable range of microbes in our environment, B cells have evolved the ability to mutate their antibody genes randomly until they produce one that sticks strongly to the invader. At that point, the 'successful' B cells proliferate and flood the system with these new antibodies.

This 'high affinity antibody' generation occurs very rapidly within specialised environments in the lymph system known as 'germinal centres'. Most of the time, germinal centres serve us well, helping us fight disease and build up a protective armory for the future.

Unfortunately, the urgency and speed at which B cells mutate within the germinal centre, as well as the random nature of the process, creates a unique problem. Sometimes the antibody created to fight the invader, or 'antigen', also happens to match 'self' and has the potential to cause autoimmune attack.

Dr Tyani Chan and Associate Professor Robert Brink from Sydney’s Garvan Institute of Medical Research developed sophisticated mouse models to investigate when and how this happens. They demonstrated that when antigen is abundant and generally available throughout the body, rogue autoantibody-generating B cells are deleted and autoimmunity avoided. Conversely, when target antigen is located only in a tissue or organ remote from the germinal centre, B cells capable of reacting against both antigen and 'self' are able to escape the germinal centre and produce autoantibodies. Their finding is published in the prestigious international journal Immunity.

"Essentially we've shown there's a big hole in self-tolerance when it comes to cross-reactive autoantibodies that can attack organ-specific targets," said Brink.

"Our finding explains a lot about how autoimmune conditions that target particular organs such as the heart or nervous system could develop after an infection. It also suggests that if you know enough about the disease and the molecular messaging systems involved, it may be possible in future to modulate the germinal centre response."

The team will continue to use their new mouse model to study the various molecular reactions involved in the progression of an autoimmune response.

Study documents eating of soil, raw starch in Madagascar

Pica—craving and intentionally consuming nonfood substances, such as earth—and amylophagy, eating raw starches—are widespread among people around the world, including the U.S. Some 180 species of animals are also known to engage in pica, possibly to rid themselves of toxins.

A study appearing Oct. 17 in the online journal Public Library of Science One provides the first population-level data of pica in Madagascar. It is one of only a few studies to assess the consumption of earths, raw starches, chalk, ash and other nonfoods across men, women and children.


Pica has been documented throughout history; it was first referenced by Hippocrates in 400 B.C. Since then, there have been hundreds of ethnographic descriptions of pica and dozens of epidemiologic studies, mostly among pregnant women, with a few studies among children.

In contrast to prior studies, this one in northeastern Madagascar found a high prevalence of pica and amylophagy among men, with some 63 percent of adult males engaging in the behavior among the 760 participants from the Makira Protected Area. Also contrary to other findings, this survey, made in 2009, found no peak in pica and amylophagy among pregnant women, though only four pregnant women were sampled. Local taboos against talking about pregnancy prior to birth may have led to underreporting, according to the authors.

The findings for men and pregnant women in Madagascar "fly against much of what I know in terms of distribution" among members of a population, said Sera Young, a research scientist in Cornell University's Division of Nutritional Sciences and the paper's senior author. Young is also the author of the book, "Craving Earth: Understanding Pica—the Urge to Eat Clay, Starch, Ice and Chalk" (2011).

Across the entire sample in the prior year, 53.4 percent engaged in geophagy, eating specific types of earth, including a fine white clay subsoil, fine sand and red river sediment; 85.2 percent ate such raw
starches as raw cassava, raw sweet potato, uncooked rice and another local wild root; and 19 percent ate other items considered locally to be nonfood, including rock salt, used coffee grounds, charcoal, rice chaff, blackboard chalk and ash.

Pica has positive and negative consequences, making it an important public health concern, said Young.

On the positive side, clay-based pica may be protective, by coating the intestines or binding directly to toxins and pathogens, thereby preventing them from entering the blood, Young added. Clay also acts as an anti-diarrheal. Such protections may be especially beneficial to vulnerable populations like pregnant women and children. Another potential benefit is that earth-based pica may act like a multivitamin, adding micronutrients like iron or calcium to the diet, which may help explain why men consume it. However, the bioavailability of these micronutrients has been shown to be very low.

On the negative side, earth, starch or other pica substances could bind to iron in the diet, leading to or worsening anemia. Also, some raw starches are high in calories but are not nutritious. And some substances may contain pathogens or harmful chemicals.

"It could be a really harmful behavior, which causes anemia, for example, or it could be a low-tech protective behavior," said Young.

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**Report: Uganda’s Speaker Promises To Pass Anti-Homosexuality Bill in Two Weeks**

**Jim Burroway**

**November 12th, 2012**

Warren Throckmorton found this report, which suggests that Uganda’s Parliament may pass proposed Anti-Homosexuality Bill sometime in the next two weeks. According to the report:

Speaker (Rebecca) Kadaga committed herself during a meeting with a coalition of religious, political, cultural leaders held at parliament where she said that Uganda is an independent country which operates under its constitution. We should stop dancing on the tune of western countries. We have the right to reject any things which is against our culture.

"Am going to allow Hon Bahati to proceed with his bill and make sure that it is passed within the period of two weeks. As leaders we should listen to the voice of our people. It is our responsibility to protect our country against homosexuality, our value, culture and character" Speaker Kadaga noted

Elsewhere religious, cultural and political leader said that all homosexual practitioners in Uganda should be killed because homosexual is not allowed in Uganda.

"It is an abomination in Uganda for a man to marry a fellow man and a woman to get married to her fellow woman. We strongly condemn and oppose the devil called homosexuality on our soil. As religious, cultural leaders we urge the Uganda’s brave (Kadaga) to be strong, farm and courageous while fighting Homosexual in Uganda. The Western world should take their moral behaviors away from Africa Uganda in particular” Religious leaders noted.

I am not familiar with Uganda Picks, so I can’t comment on the report’s veracity. Warren Throckmorton writes, “the basic news that the Parliament is set to act on the bill is consistent with what I am hearing from sources in Uganda." It also confirms a report made earlier this month by Daily Monitor, a much more reputable independent newspaper, which quoted the Legal and Parliamentary Affairs Committee Chair Steven Tashobya as saying that his committee will be ready to report the bill back to the House floor before Parliament breaks for Christmas.

**Update: The Associated Press** is now picking up on the story:

Ugandans "are demanding it," (Kadaga) said, reiterating a promise she made before a meeting on Friday of anti-gay activists who spoke of "the serious threat" posed by homosexuals to Uganda’s children. Some Christian clerics at the meeting in the Ugandan capital, Kampala, asked the speaker to pass the law as "a Christmas gift."

"...Who are we not to do what they have told us? These people should not be begging us," Kadaga said of activists who want the bill to become law."

M.P. David Bahati, the bill’s sponsor, now chairs the ruling party’s caucus in Parliament. But unlike in previous periods of intense discussions about the bill, his present media silence has been conspicuous. Kadaga, a long-time supporter of the bill, appears to have taken the public role of pushing for the bill’s passage. In early 2009, she advocated for for increased criminal penalties for homosexuality. She presided over Parliament in April 2009 in her role as Deputy Speaker when MP David Bahati sought approval to submit an Anti-Homosexuality Bill as a private member’s bill, and she was an early supporter after it was first introduced into Parliament in October. After the previous parliament expired
before it could bring the bill up for a vote, Kadega helped engineer the bill’s reintroduction, with the death penalty intact, in the current Parliament.

If the bill does come back up for a vote, past experience suggests that there will be a great deal of misinformation about what the bill would do. I would suggest you keep these links handy:

Clause By Clause With Uganda’s Anti-Homosexuality Bill:
Clauses 1 and 2: Anybody Can Be Gay.
Clause 3: Anyone Can Be “Liable To Suffer Death.”
Clause 4: Anyone Can “Attempt to Commit Homosexuality”
Clauses 5 and 6: Anyone Can Be A Victim (And Get Out Of Jail Free If You Act Fast)
Clauses 7 and 14: Anyone Can “Aid And Abet”
Clauses 8 to 10: A Handy Menu For “Victims” To Choose From
Clauses 11, 14, 16 and 17: Nowhere To Run, Nowhere To Hide
Clause 12: Till Life Imprisonment Do You Part
Clause 13: The Silencing of the Lambs
Clause 14: The Requirement Isn’t Only To Report Gay People To Police. It’s To Report Everyone.
Clauses 15 and 19: The Establishment Clauses For The Ugandan Inquisition

Grape Seed Extract Bollixes Norovirus
ScienceDaily (Nov. 8, 2012) — Norovirus causes more than half of all food-born illnesses in the United States, and is the second greatest source of reported food borne illness outbreaks in the European Union. A recent study found that grape seed extract could reduce the infectivity of Norovirus surrogates (Norovirus surrogates are viruses that share pathological and/or biological features with human norovirus). Now, Dan Li of Ghent University, Ghent, Belgium and collaborators have shown that grape seed extract does so by denaturing the capsid protein, which is the coat of the virus, thereby disabling the virus.

The research is published in the November 2012 issue of Applied and Environmental Microbiology. In the study, the researchers observed that under treatment with grape seed extract, at low doses, the spherically-shaped murine (mouse) norovirus-1 coat proteins clumped, and showed "obvious deformation and inflation," according to the report. At higher doses, the researchers saw no coat proteins, only protein debris. "This provides evidence that [grape seed extract] could effectively damage the [norovirus] capsid protein, which could reduce viral binding ability and infectivity accordingly," according to the report.

The researchers used surrogate viruses because there are no suitable animal models of norovirus, and human norovirus has been impossible to propagate in cell cultures. The surrogate virus, murine norovirus-1, can be grown in cell culture, and belongs to the same genus as human norovirus, and has a very similar genome structure, and morphology. Nonetheless, the researchers were able to measure the specific binding strength of human norovirus by two different methods, finding that it declined precipitously under the influence of grape seed extract, providing further support to their results.

Norovirus is transmitted mainly fecal-orally, and infected food handlers, contaminated water, and surfaces can be identified as important sources of transmission, "which could further contaminate ready-to-eat foods, drinking water, shellfish, and fresh produce,” says Li. A mere 10-100 virus particles are sufficient to transmit the disease.

Journal Reference:

Kabul’s Sex Workers Get Organized
Prostitutes in Kabul, the capital of Afghanistan, have organized into an underground self-help network to avoid detection by the state, stop the spread of disease, and identify abusive customers. The world of prostitution by women and men in Afghanistan is hidden, solely known anecdotally through the sex workers themselves. In Afghanistan, adulterers can be stoned to death, and the sexes are exactly segregated. Sex workers have particular risks in this country where sex education is practically nonexistent, and families generally kill female relatives for acts such as premarital sex. One female prostitute has been visiting beauty salons, often fronts for the prostitution trade, to teach other prostitutes about using condoms and getting tested for STDs.

Male prostitutes also are at great risk for violent attacks and have little recourse. According to General Mohammed Zaher, head of the police criminal investigation department, the Kabul police force is “cracking down on crimes” such as alcohol consumption, gambling, sodomy, and prostitution. Convicted
prostitutes usually face six-month jail sentences. Though solicitation is illegal, their clients tend not to be arrested. However the sex trade remains busy in Kabul, and is estimated to include 6,000 female and 4,000 male prostitutes, although these numbers are not confirmed.

The prostitutes’ self-help group uses a compartmentalized phone tree, in which each person is responsible for notifying an assigned list of people. Within the group, peer educators teach fellow sex workers about condoms and STD prevention. HIV is rare in Afghanistan, and none of the sex workers in the network have tested HIV-positive, according to the doctors who conducted the tests; however, other STDs are a problem, specifically hepatitis C, which is endemic in Afghanistan. Kabul prostitutes distribute literature that emphasizes the risk of contagion with unprotected sex. Their pamphlets also emphasize regular testing. Even the doctors who perform the testing are reluctant participants. They are only being employed because they cannot find other work; they risk the community’s wrath and possible attack if their participation in testing sex workers is discovered.

**Lipid Levels Increased for Patients on Suppressive ART Regimen**

*Healio*, (11.12.2012)

A study by David A. Kamara of the University College London and colleagues found that persons with HIV infection on a regimen of suppressive antiretrovirals have high levels of total cholesterol, HDL cholesterol, and triglycerides.

The researchers investigated the effects of ART, HIV viremia, and immunosuppression on levels of total cholesterol, HDL cholesterol, and triglycerides in participants of the Data Collection on Adverse Events of Antiretroviral Drugs (DAD) study. At, or soon after, enrollment in the study, 91 percent of the 50,000 participants supplied a total cholesterol measurement, 89 percent provided a triglyceride measurement, and 78 percent an HDL measurement.

Data show that participants who were off ART had lower lipid levels compared with those on ART and had a suppressed viral load. Non-suppressive ART was associated with lower levels of total cholesterol and HDL cholesterol, but did not affect triglycerides. A low current CD4 count was also associated with lower lipid levels, and the lowest CD4 count was associated with higher total cholesterol and triglyceride levels. Also, patients with a prior AIDS diagnosis had higher total cholesterol and triglyceride levels, but lower HDL cholesterol levels.

The higher total cholesterol and triglyceride and lower HDL cholesterol levels among those with the lowest level CD4 count and with a previous AIDS diagnosis suggests severe immunosuppression may be associated with dyslipidemia. Three-quarters of the participants were men, three-quarters did not have AIDS, and half were white. Participants’ treatment history showed that 61 percent had prior experience with ART, 47 percent had experience with protease inhibitors, 61 percent with nucleotide reverse transcriptase inhibitors, 29 percent with non-nucleoside reverse transcriptase inhibitors, and 4 percent were not receiving anti-lipid drugs. Kamara concluded that lipid levels were considerably higher for participants on a suppressive ART regimen. He stated that future longitudinal analyses will consider the impact of specific ARTs and the duration of ART on lipid levels.

The report was presented at HIV11 Congress; Nov. 11–15, 2012, in Glasgow Scotland.

**U.N. Has 'Moral Responsibility' To Address Cholera Outbreak In Haiti**

Sometimes "[w]hen the international aid community descends on a vulnerable place ... good intentions make a bad situation even worse," a Boston Globe editorial states, adding that is "what happened two years ago, when United Nations peacekeepers arrived in Haiti in the wake of a devastating earthquake, bringing the deadly disease cholera with them." According to a panel of U.N. experts, poor sanitation in the peacekeepers’ camp likely caused the outbreak, which has killed 7,000 people and sickened 500,000, the editorial notes. "So far, the United Nations has declined to apologize for its role, or even admit it—perhaps because it is facing a deluge of expensive legal claims brought by the Boston-based Institute for Justice & Democracy in Haiti on behalf of the victim’s families," the editorial states, noting that after a year, the "U.N. says it is still studying the claims."

"But foot-dragging is the wrong response," the Boston Globe continues, adding, "The institute's foremost demand is not monetary compensation for cholera victims, but U.N. action to stop the disease from spreading; this would involve a massive investment in clean water and sanitation infrastructure" that would help reduce cholera and other water borne diseases. Though expensive, the U.N. could generate some funding for the project by sending peacekeepers home early from Haiti, the editorial says, concluding, "The U.N. has a moral responsibility to correct its mistakes in Haiti and to institute simple
public health protocols to ensure that peacekeepers who hail from cholera-infected areas never spread the disease again” (11/13).

**Experts report 1 of 2 remaining types of polio virus may be eliminated in Pakistan**  
But researchers, reporting at ASTMH annual meeting, also cite barriers to complete elimination from a surge of cases in Nigeria to intensifying vaccine refusals in Pakistan

ATLANTA (November 13, 2012)—Polio cases worldwide reached historic lows in 2012, and for the first time there were no new outbreaks beyond countries already harboring the disease, leaving researchers confident that a massive and re-energized international campaign to eradicate polio is on a path to success, according to presentations today at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH).

Globally there were 177 polio cases through October 2012, a drop from 502 during the same period last year.

Despite the dramatic drop, polio experts noted challenges in Pakistan posed by parents who refuse to vaccinate their children and in Nigeria where polio cases more than doubled in 2012 and threatened to re-infect currently polio-free countries. Pakistan, Nigeria and Afghanistan are the only countries where polio remains endemic and are the battle grounds of efforts to make polio only the second human disease, after smallpox, to be completely eliminated.

Steven Wassilak, MD, a medical epidemiologist and polio expert at the US Centers for Disease Control and Prevention (CDC), said new data from Pakistan show that of the two types of wild polio virus (WPV1 and WPV3) circulating in the country, the one known as WPV3—or Type 3—is close to being eliminated.

"There have not been any Type 3 cases reported for six months, which is the longest gap in incidence there to date," he said. "CDC works with Pakistan officials to monitor different chains of transmission over time and Type 3 is now down to only one chain, which is an indication that we are close to breaking the last link of Type 3."

CDC, which has led the effort to establish a global network of laboratories to track and sequence the genome of the wild polio virus, is one of four partners spearheading the Global Polio Eradication Initiative along with Rotary International, UNICEF and the World Health Organization (WHO), with great support from the Bill and Melinda Gates Foundation. In September, the partners along with leaders from Pakistan, Nigeria, and Afghanistan met at United Nations Headquarters in New York to reaffirm the Emergency Action Plan against polio, launched in May. The initiative includes a "surge of human resources" involving 4,000 people who have been deployed to complete the eradication effort.

**New Study Finds Vaccine Refusals Remain Barrier to Elimination**

At the ASTMH conference, Anita Zaidi, MD, a pediatrician at Aga Khan University in Karachi who serves on Pakistan's National Immunization Technical Advisory Group, is presenting new data showing that while Pakistan has made major progress against polio by expanding immunization campaigns, the remaining challenge is not one easily solved by additional resources.

"We found that in Karachi, a key reason children fail to get immunizations is not due to lack of access, but because their parents refuse to participate," Zaidi said. "That is a big challenge and not something that can be overcome only by expanding immunization campaigns."

In a study published in the Bulletin of the World Health Organization (WHO), Zaidi and her colleagues found that in Karachi, "parent refusal was the most common reason given for the failure of children to participate in two recent polio supplementary immunization activities," accounting for 74 percent of missed immunizations.

While opposition to polio vaccinations has been widely reported in the remote, restive tribal territories in the north, less examined, Zaidi said, has been the situation in the urban environs of Karachi, which her study describes as "the only megacity in the world that has not succeeded in interrupting polio transmission." Nationwide, Pakistani health officials believe vaccine refusals, driven by false rumors that immunizations cause sterility and are contaminated with HIV, actually are declining. But Zaidi said that recent events in Karachi suggest the intensity of those who remain opposed appears to be rising.

She pointed out that in just the last few months, a health worker in Karachi involved in the polio campaign was killed and the child of another was kidnapped (though later returned unharmed). Zaidi said that she recently participated in a polio seminar in Karachi where concerns about violence prompted the organizers to avoid any publicity. Given the current volatile environment and continued evidence of widespread viral transmission in sewage sampling, Zaidi said that while Pakistan is making considerable progress in reducing polio cases, eradication by 2013 appears unrealistic.
"Efforts should focus on building trust through grassroots efforts using community elders in populations with high vaccine refusal rates," she said. By providing vaccination at mass transit sites such as bus routes used to travel up-country throughout the year, we can at least isolate the viral reservoirs and make sure we avoid what happened last year, which was exporting the virus to China."

**In Nigeria, Working With Traditional Leaders, Nomadic Groups**

Meanwhile, opposition to immunizations is also a major challenge in Nigeria, where the number of polio cases has risen for the second straight year, said Adamu Nuhu, MD, with Nigeria's National Primary Healthcare Development Agency. He said cases are at least confined to the northern part of the country where opposition to immunizations is rooted in religious or political differences and, as in Pakistan, has been stirred by rumors of vaccine-induced sterilization and HIV infection.

"We are working now with traditional leaders in the north who are respected by local people to change the perceptions of polio immunization and encourage more participation in immunization efforts," Nuhu said. "There is evidence that overall, immunization rates among children at risk are rising to 80 percent."

He described a campaign that is now literally going house-to-house to identify family decision makers and talk with them about the importance of polio immunization. Also, health officials—who are working closely with international partners including the WHO, UNICEF and the CDC—are pursuing new strategies to improve immunization coverage in nomadic groups.

"Even though they are often moving, they have a leadership structure and we can work through these leaders to provide polio immunizations," Nuhu said. "But we understand that you will not be able to immunize any children unless you can reach them on their pastoral routes and camps."

The persistence of polio in Nigeria—in 2012 the country has documented 99 cases—is especially worrisome because cases in Nigeria have spread in the past to Sudan, Chad, and 23 other countries. All these countries are now once again polio-free except for Chad. The CDC reported in October that Chad could interrupt wild polio transmission by the end of this year, but that failure to stop transmission in Nigeria could prompt new outbreaks.

**Vaccine Refusal: Lessons from India?**

The CDC's Wassilak said the refusal by parents in Pakistan and Nigeria to vaccinate their children presents a challenge to eradication. "Karachi is a densely populated area where you need a high degree of immunity to interrupt polio transmission, so every child counts," he said.

But Wassilak said vaccine refusal is not an insurmountable barrier to global eradication.

"We saw similar problems in India, and while they were not resolved overnight, eventually we saw immunization coverage increase and polio cases halted," he said. "It requires working more closely with community leaders and greater political commitment at all levels, which is what we are seeing in both Pakistan and Nigeria."

India has not reported a polio infection since January 2011 and the entire Southeast Asia Region of WHO could be certified polio-free in 2014 if no new cases arise. Wassilak said advisors from India are now working in Nigeria to share their lessons learned. Meanwhile, the CDC is providing technical support to the global eradication effort, tracking the different types of polio that are circulating in the affected countries and training volunteers to assist in polio vaccination campaigns.

"This urgent international push for polio eradication means that soon no child will be hurt by this disease. The relentless drive to alleviate pain and suffering is the spirit of this Society and permeates every session and every hallway conversation at this meeting," said ASTMH President James W. Kazura, MD, FASTMH. "We will get this done."

**Scientists report injectable formulation of malaria parasites achieve controlled infection**

Speaking at ASTMH Annual Meeting, researchers say breakthrough could make it much easier to evaluate new drugs and vaccines while also becoming a vaccine itself

ATLANTA (November 13, 2012) In a breakthrough that could accelerate malaria vaccine and drug development, scientists announced today that, for the first time ever, human volunteers were infected with malaria via a simple injection of cryopreserved sterile parasites that were harvested from the salivary glands of infected mosquitoes in compliance with regulatory standards. The parasites had been frozen in a vial for more than two years.

The established gold standard for deciding whether or not to proceed with the development of a new malaria drug or vaccine is known as a "human challenge" trial, in which volunteers exposed to the vaccine
or experimental drugs are deliberately subjected to bites from infected mosquitoes. The findings from this study indicate that direct injection of cryopreserved parasites can be used in lieu of mosquito bites.

In a presentation at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH), researchers at Radboud University Medical Center in the Netherlands and their colleagues from Sanaria Inc. and Protein Potential LLC said the findings from this study eventually could lead to a powerful tool for testing promising malaria drugs and vaccines in trials that involve deliberately exposing subjects to a "controlled human malaria infection" (CHMI). Also, they said the injectable formulation of malaria parasites might be considered, by itself, as part of a novel approach to providing protection against a disease that each year kills at least 650,000 people, most of them young children in Africa. The findings were also published today online in the American Journal of Tropical Medicine and Hygiene and will be published in the January 2013 print issue.

"Our study shows it's possible to manufacture and then administer controlled doses of malaria parasites using a needle and syringe to deliver a formulation that can meet regulatory standards for purity and dose consistency," said Meta Roestenberg, MD, of the Radboud University Nijmegen Medical Center and the lead author of the study along with Else M. Bijker, MD.

The current "human trial challenge" method is technically complex and costly, and there are only a few places in the world today where such work is being done. Also, when using mosquitoes to deliver malaria parasites (or "sporozoites" as they are called when they first invade the human body), it can be difficult to ensure that all subjects receive the same level of infection. And scientists say that can influence the outcome of the treatment.

In a controlled human malaria infection trial, conducted at Radboud University Medical Center from October 2010 to July 2011, researchers injected eighteen healthy Dutch volunteers with cryopreserved Plasmodium falciparum malaria sporozoites (PfSPZ Challenge). The study showed that 84% of participants – five of the six volunteers in each group – were safely and successfully infected with no differences among the groups in the time it took for the infection to develop or the presentation of symptoms. The volunteers who developed infections subsequently received treatment and quickly recovered without incident.

"We have demonstrated the potential to develop what you might call the human challenge trial in a bottle that could be available to scientists anywhere who need to know how a new drug or vaccine would fare against a real but carefully controlled and calibrated malaria infection," said Stephen L. Hoffman, MD, chief executive and scientific officer of Sanaria Inc. and the study's co-senior author. "This accessibility could be particularly important for expanding malaria research capabilities at African research centers, which is critical to combating this resilient disease."

The authors of the study also said that the results could provide evidence for developing what are known as "whole parasite" vaccines. Robert W. Sauerwein, MD, PhD, of Radboud University Medical Center said that the new study showing that infections could be accomplished with a simple shot in the arm could make the whole parasite approach more feasible.

"A major challenge to realizing the potential of whole parasite vaccines is the development of a stable, consistent formulation of sporozoites that can be manufactured, preserved and used like any other vaccine," said Sauerwein, the study's other senior author.

Sanaria is currently pursuing clinical trials to test two different approaches to whole parasite vaccination—irradiated sporozoites and inducing controlled infections in tandem with the administration of anti-malaria drugs. Also, researchers are planning additional trials to ensure the infection produced with the cryopreserved sporozoites mirrors what one would experience through bites from infected mosquitoes.

"This study is a great example of the innovative and dynamic research being done through partnerships across academic and corporate sectors that's translating research into needed tools to control and ultimately eradicate malaria," said James Kazura, president of the American Society of Tropical Medicine and Hygiene. "What we have here is a new avenue, a new clue to study how the infection develops, and with that we are moving closer to eliminating what is truly a global scourge."

**Common enzyme deficiency may hinder plans to eradicate malaria**

Press release from PLOS Medicine

In malaria-endemic countries, 350 million people are predicted to be deficient in an enzyme that means they can suffer severe complications from taking primaquine, a key drug for treating relapsing malaria, according to a study funded by the Wellcome Trust and published in this week's PLOS Medicine.
This finding is important as primaquine is recommended in the global action plan to eliminate malaria and is the only drug to prevent malaria relapse. The benefits of implementing a treatment program with this drug need to be weighed against the potential harm to a substantial proportion of the population (up to 8%) who may have G6PD deficiency: a genetic defect reducing glucose-6-phosphate dehydrogenase enzyme activity. Individuals with G6PD deficiency who are given primaquine can experience a severe complication – the breakdown of their red blood cells (hemolysis).

The authors from Indonesia, Kenya, the Philippines, and the United Kingdom, led by Rosalind Howes from the University of Oxford, reached these conclusions by inputting information about the frequency of G6PD deficiency from community surveys into a geostatistical model. Using the model, the authors predicted that G6PD deficiency is widespread across malaria-endemic regions, with the lowest frequencies in North and South America and the highest frequency in tropical Africa and the Arabian Peninsula.

Dr Howe explains: "Malaria control and elimination are a top priority on the global health agenda. Yet, a key drug to help achieve this goal remains too dangerous for widespread use. We have developed a map of this risk factor, G6PD deficiency, and find it to be very common across many malaria endemic regions. Much work remains to be done to fully understand this disease, notably its genetic diversity."

The authors found that the predicted frequency of G6PD deficiency varied considerably over relatively short distances in many areas but the overall frequency was 8% in malaria-endemic countries, corresponding to about 350 million affected individuals. In countries that are currently planning to implement malaria elimination programs, the frequency was 5.3%, corresponding to 100 million affected individuals.

When the authors took the severity of the G6PD deficiency (the more severe the deficiency, the higher the risk of hemolysis), they found that the greatest risk was across Asia, where severe G6PD variants are commonly inherited.

The authors say: The prominence of G6PD deficiency represents a barrier to current options for malaria elimination therapy."

They continue: "The complexity and diversity of both malaria epidemiology and G6PD deficiency mean that no single solution will be applicable for ensuring safe and effective primaquine treatment."


Western media coverage of female genital surgeries in Africa called 'hyperbolic' and 'one sided'
Network of doctors, scholars, and feminists criticizes major studies and makes recommendations; commentators take issue with interpretations and conclusions
Despite widespread condemnation of female genital surgeries as a form of mutilation and a violation of human rights, an international advisory group argues that the practice is poorly understood and unfairly characterized. In a public policy statement in the Hastings Center Report, the Public Policy Advisory Network on Female Genital Surgeries in Africa, a group that includes doctors, anthropologists, legal scholars, and feminists, argues that media coverage of the practice is hyperbolic and one sided, "painting the now familiar portrait of African female genital surgeries as savage, horrifying, harmful, misogynist, abusive, and socially unjust."

The advisory network’s statement takes no position on whether the practice should continue. It aims to "move the coverage of the topic from an over-heated, ideologically charged, and one-sided story about 'mutilation,' morbidity, and patriarchal oppression to a real, evidence-based policy debate governed by the standards of critical reason and fact checking."

Three commentaries responding to the article, written by three bioethicists and an obstetrician-gynecologist, also appear in the journal.

Female genital surgery -- a neutral term used by the advisory network instead of other terms, such as female genital cutting and female circumcision -- has been condemned as a violation of the human rights of girls and women by a wide range of experts and organizations, including the World Health Organization and the United Nations. In several African countries, including Egypt, Guinea, Sierra Leone, and Somalia, more than 90 percent of women ages 15 to 49 have undergone such surgeries.

In its statement, the advisory network focuses mainly on two types of female genital surgery, which they state comprise 90 percent of procedures in Africa. These practices involve reducing the clitoral
hood and tissue and reducing or eliminating the labia and the clitoris. A third type, referred to as infibulation or sealing, involves narrowing the vaginal opening with stitches or some other sealing method.

The authors put forth seven facts that they hope will change the scope of media coverage and lead to a better understanding of the cultural complexities underlying female genital cutting:

- Medical research has found that a high percentage of women who have had genital surgery "have rich sexual lives, including desire, arousal, orgasm, and satisfaction, and their frequency of sexual activity is not reduced."
- Reproductive health and medical complications linked to female genital surgery happen infrequently.
- Those who value female genital surgery view it as aesthetic enhancement, not mutilation.
- In almost all societies where female genital surgery is performed, male genital surgery also takes place. Broadly speaking, then, such societies "are not singling out females as targets of punishment, sexual deprivation, or humiliation."
- The link between patriarchy and female genital surgery is unfounded. Almost no patriarchal societies adhere to the practice and, at the same time, the practice is not customary in the world's most sexually restrictive societies.
- Women manage and control female genital surgery in Africa and the practice "should not be blamed on men or on patriarchy." Ironically, the authors contend, groups that fight against female genital surgery weaken the power of women.
- An influential WHO study about the "deadly consequences" of female genital surgery is the subject of criticism that has not been adequately publicized. The reported evidence does not support sensational media claims about female genital surgery as a cause of perinatal and maternal mortality during birth.

The authors outline the following seven policy implications:

- The media, activists and policy-makers must "cease using violent and preemptive rhetoric" that paints a sensational image of African parents mutilating their daughters and damaging their reproductive and sexual health.
- It should be acknowledged that female genital surgery is not unique to African women; the authors liken it to "genital piercings on college campuses" and "vaginal rejuvenations requested by some Western women."
- Advocates fighting for safe, hospital-based female genital surgery should be given a voice in public policy forums.
- "Zero tolerance" slogans promoted by anti-mutilation groups are counterproductive. Not only do they limit thoughtful, respectful dialogue, but they can make genital surgery more dangerous by driving the practice underground.
- Legislation and regulations that criminalize female genital surgery for adult women are discriminatory, because they deny women's autonomy "to choose what makes them happy with their own bodies."
- Studies of genital surgery should be multidisciplinary, and there should be support for a network linking researchers and advocates who have diverse points of view.
- Women and girls who have undergone genital surgery as children and are now living in countries where the practice is nonexistent or illegal should not be subjected to discourse that stigmatizes them or teaches them to expect sexual dysfunction. Such discourse "may provoke what could be called 'psychological mutilation,'” potentially compromising the development of a normal and healthy psychosexual life.

While agreeing with the international network's call for accurate information about female genital surgery and its criticisms of inflammatory language, three commentaries disagree with the policy advisory statement.

Ruth Macklin, a bioethicist and professor in the department of epidemiology and population health at the Albert Einstein College of Medicine of Yeshiva University, takes issue with its depiction of the facts and points to crucial information that is missing from the statement, including numerous statements and resolutions by the International Federation of Gynecology and Obstetrics opposing the performance of female genital cutting and opposing any efforts to medicalize the procedure, and studies documenting...
significant harm to women who have undergone the procedure, as well as a change in attitude among younger women in countries where the prevalence of female genital cutting is high.

In another commentary, Nikola Biller-Andorno, director of the Institute of Biomedical Ethics at the University of Zurich, and Verina Wild, the institute's deputy director, argue that enough evidence now exists to define the conditions under which female genital cutting is morally unacceptable. They state that it would be unimaginable to conduct a randomized, controlled trial of the practice or to undertake long-term cohort studies, because such research would in fact condone female genital cutting. "Requiring more data before committing to a stance against clearly unacceptable forms of female genital cutting is not a proof of neutrality," they conclude. "It means failing to protect a very vulnerable population." The authors also call into question the Advisory Network's depiction of women's autonomy, suggesting instead that women may be compelled to undergo female genital cutting, because they cannot deviate from their local customs and social structures.

In the third commentary, Dr. Nawal M. Nour, an obstetrician-gynecologist and director of the African Women's Health Center (AWHC) at the Brigham and Women's Hospital in Boston, writes that her patients have endured both major and minor long-term complications from female genital cutting. Nour also states her concern that the Advisory Network's presentation of data is biased. For example, she writes that the statement that "a high percentage of women have rich sexual lives" would be more plausible if "high" were changed to "some." Nour cites a large meta-analysis showing that "women who had undergone genital cutting were more likely to report dyspareunia, no sexual desire, and less sexual satisfaction." "Speaking as both an African woman and an obstetrician-gynecologist," she writes, "I hope that this practice ends during my lifetime."

**High Exposure to Food-Borne Toxins: Preschool Children Particularly Vulnerable to Compounds Linked to Cancer, Other Conditions**

ScienceDaily (Nov. 13, 2012) — In a sobering study published in the journal *Environmental Health*, researchers at UC Davis and UCLA measured food-borne toxin exposure in children and adults by pinpointing foods with high levels of toxic compounds and determining how much of these foods were consumed. The researchers found that family members in the study, and preschool children in particular, are at high risk for exposure to arsenic, dieldrin, DDE (a DDT metabolite), dioxins and acrylamide. These compounds have been linked to cancer, developmental disabilities, birth defects and other conditions. However, the study also points to dietary modifications that could mitigate risk.

"Contaminants get into our food in a variety of ways," said study principal investigator Irva Hertz-Picciotto, professor and chief of the Division of Environmental and Occupational Health at UC Davis. "They can be chemicals that have nothing to do with the food or byproducts from processing. We wanted to understand the dietary pathway pesticides, metals and other toxins take to get into the body."

Researchers assessed risk by comparing toxin consumption to established benchmarks for cancer risk and non-cancer health risks. All 364 children in the study (207 preschool children between two and seven and 157 school-age children between five and seven) exceeded cancer benchmarks for arsenic, dieldrin, DDE and dioxins. In addition, more than 95 percent of preschool children exceeded non-cancer risk levels for acrylamide, a cooking byproduct often found in processed foods like potato and tortilla chips. Pesticide exposure was particularly high in tomatoes, peaches, apples, peppers, grapes, lettuce, broccoli, strawberries, spinach, dairy, pears, green beans and celery.

"We focused on children because early exposure can have long-term effects on disease outcomes," said Rainbow Vogt, lead author of the study. "Currently, the U.S. Environmental Protection Agency only measures risk based on exposures of individual contaminants. We wanted to understand the cumulative risk from dietary contaminants. The results of this study demonstrate a need to prevent exposure to multiple toxins in young children to lower their cancer risk."

The researchers used data from the 2007 Study of Use of Products and Exposure-Related Behavior (SUPERB), which surveyed households in California with children between two and five to determine how their diets, and other factors, contribute to toxic exposure. Specifically, SUPERB homed in on 44 foods known to have high concentrations of toxic compounds: metals, arsenic, lead and mercury; pesticides chlorpyrifos, permethrin and endosulfan; persistent organic pollutants dioxin, DDT, dieldrin and chlordane; and the food processing byproduct acrylamide. Toxin levels in specific foods were determined through the Total Diet Study and other databases.
Perhaps most disturbing, preschool-age children had higher exposure to more than half the toxic compounds being measured. Even relatively low exposures can greatly increase the risk of cancer or neurological impairment.

"We need to be especially careful about children, because they tend to be more vulnerable to many of these chemicals and their effects on the developing brain," says Hertz-Picciotto.

Though these results are cause for concern, the study also outlines strategies to lower family exposure. For example, organic produce has lower pesticide levels. In addition, toxin types vary in different foods. Certain pesticides may be found in lettuce and broccoli, while others affect peaches and apples.

"Varying our diet and our children's diet could help reduce exposure," said Hertz-Picciotto. "Because different foods are treated differently at the source, dietary variation can help protect us from accumulating too much of any one toxin."

Families also can reduce their consumption of animal meat and fats, which may contain high levels of DDE and other persistent organic pollutants, and switch to organic milk. While mercury is most often found in fish, accumulation varies greatly by species. Smaller fish, lower on the food chain, generally have lower mercury levels. In addition, acrilomides are relatively easy to remove from the diet.

"Acrilomides come from chips and other processed grains, said co-author Deborah Bennett, associate professor of Environmental and Occupational Health at UC Davis. "Even if we set aside the potential toxins in these foods, we probably shouldn't be eating large amounts of them anyway. However, we should be eating fruits, vegetables and fish, which are generally healthy foods. We just need to be more careful in how we approach them."

The study also highlights a number of policy issues, such as how we grow our food and the approval process for potentially toxic compounds. Though the pesticide DDT was banned 40 years ago, the study showed significant risk of DDE exposure.

"Given the significant exposure to legacy pollutants, society should be concerned about the persistence of compounds we are currently introducing into the environment," said Bennett. "If we later discover a chemical has significant health risks, it will be decades before it's completely removed from the ecosystem."

While the study has profound implications for dietary habits, more work needs to be done to quantify risk. Specifically, researchers need to determine how these food-borne toxins interact collectively in the body.

**Journal Reference:**

**Scientists Question Designation of Some Emerging Diseases**

ScienceDaily (Nov. 13, 2012) — The Ebola, Marburg and Lassa viruses are commonly referred to as emerging diseases, but leading scientists say these life-threatening viruses have been around for centuries.

In a perspective in the Nov. 9 issue of the journal *Science*, researchers including a professor at The University of Texas Health Science Center at Houston (UTHealth) say it would be more appropriate to refer to these viruses as emerging diagnoses.

"The infectious agents were identified around the middle of the 20th century but that does not mean that they were new," said Joseph McCormick, M.D., one of the authors of the perspective and regional dean of The University of Texas School of Public Health Brownsville Regional Campus, which is part of UTHealth. "Some of the viruses, including Lassa and Ebola, have been around for thousands of years."

The viruses burst onto the scene in the 1960s when outbreaks decimated areas of west and central Africa. The viruses can lead to hemorrhagic fever, a condition characterized by bleeding, shock, vomiting and diarrhea. In severe cases, the death rate may reach 90 percent.

These viruses thrive in animals—not humans. But people can get the viruses if they come in contact with infected animals or are exposed to virus-infected fluids or tissues. Infected people are moderately contagious with person-to-person transmission only through direct contact with infectious fluids such as blood or urine. Patients with Lassa virus can be successfully treated by antiviral medications.

With the aid of epidemiologic, ecologic and genetic studies, researchers have learned that these viral hemorrhagic fevers are endemic in several areas of Africa. And, the Ebola viruses are endemic in other parts of the globe.

"The Arenavirus family of viruses that occur on many continents, of which the African Lassa virus is a member, is an ancient family of viruses that have likely evolved along with their rodent hosts over millions
of years," said McCormick, former chief of the Special Pathogens Branch of the Centers for Disease Control and Prevention.

So what would designating the viruses as emerging diagnoses mean?

"It means that these viruses have lurked as enzootic viruses in the environment and that their 'discovery' was related to the scientific capacity to make the diagnosis rather than their 'emergence,’” McCormick said. "However, it also means that we also now know more about the risks of encountering them and therefore, how to identify those who may be at risk for infection."

He said the designation would aid in the diagnosis. "Now that we understand more about their ecological niches and geographical distribution, we know more about how to avoid them. We also know more about how they cause disease and we may be able to improve treatment and seek vaccines. All of this information will lead to a more proactive approach for detection and prevention,” McCormick said.

"Antibody tests now allow public health officials to gauge the exposure of the public to these viruses.”

With this information, McCormick, the James H. Steele Professor of Epidemiology at the UT School of Public Health, said public health officials could develop strategies for prevention and mitigation of epidemics that have characterized these viruses in the past.

McCormick said that with the ease and rapidity of global transportation, it is also important for caregivers in other parts of the world to familiarize themselves with the signs and symptoms. "The symptoms in the early stages are fever, headache and nausea and can easily be misdiagnosed as the flu," said McCormick, adding that physicians need to ask about the travel history of feverish patients.

McCormick is one of the world’s foremost authorities on the Ebola and Lassa viruses. He also led the first HIV investigation in Africa and is the investigator who isolated the oldest HIV strain, which is recounted in the book, "Level 4: Virus Hunters of the CDC," which he co-authored with Susan Fisher-Hoch, M.D. She is a professor of epidemiology at the UT School of Public Health Brownsville Regional Campus. McCormick and Fisher-Hoch are also on the faculty of The University of Texas Graduate School of Biomedical Sciences at Houston.


Early Clinical Observations in the Fungal Meningitis Outbreak
ScienceDaily (Nov. 12, 2012) — A new article being published early online in Annals of Internal Medicine describes the diagnosis and treatment protocol established in a Roanoke, Va. hospital to care for dozens of patients presenting with suspected fungal meningitis related to contaminated epidural spinal injections.

This unprecedented surge of patients seeking care for a rare central nervous system (CNS) infection required physicians to react quickly with little data to guide treatment decisions. The authors suggest that the data collected from these cases may fill information gaps and inform current and future therapy for fungal meningitis patients.

Since early October, nearly 400 people nationwide have been diagnosed with fungal meningitis linked to contaminated injectable preservative-free methylprednisolone acetate used for epidural steroid injections and more than 14,000 people have been exposed. Currently, there are no clear recommendations for treatment. The Carilion Clinic in Roanoke saw half the fungal meningitis cases reported from Virginia and documented the clinical course.

The hospital established a hotline for patients concerned about infection. One-hundred-seventy-two patients presented to the emergency room and 131 met their exposure criteria for fungal meningitis due to the contaminated epidural steroid injections. After screening using lumbar punctures, 25 patients were diagnosed with fungal meningitis and were managed by Infectious Diseases services, which continually sent data on these patients to the Virginia Department of Health. An additional two patients presented to the hospital moribund following stroke, died, and were diagnosed with fungal meningitis retrospectively.

All patients were treated with IV voriconazole at a dosage of 6 mg/kg every 12 hours and continued on this treatment, unless switched to IV amphotericin-B (if symptoms or side-effects warranted). Patients remained hospitalized until oral voriconazole was available for home therapy, and continue to be seen weekly in a pop-up "fungal meningitis clinic" within the Infectious Disease outpatient clinic.

Roanoke clinicians still have questions about the nature and course of this infection. There were two patients who had symptoms of infection, but had an initial negative screening result at lumbar puncture. They returned later with meningitis, suggesting that patients will need to be followed for an undetermined duration of time. Two other patients presented with stroke and quickly died, while three other patients developed stroke during treatment, leading researchers to suspect that Exserohilum is angio-invasive.
Finally, the high number of patients complaining of "word searching" suggests that long-term neurological consequences should be a concern. The authors of an accompanying commentary acknowledge the risks associated with diagnosis and treatment of this rare CNS infection. The authors note some of the pressing questions physicians face when patients present with exposure or suspected infection. With limited knowledge of this infection, clinicians must rely on quickly evolving practice recommendations being established by the CDC and others gaining first-hand experience with this outbreak. The CDC has convened a committee of "Clinical Mycology Expert Consultants" that will consult on these cases. In the meantime, they will continue to capture data to inform recommendations.

**Journal Reference:**

**Ugandan LGBT Coalition urges extreme caution when foreigners advocate against the Anti-Homosexuality Bill**

While the Ugandan Anti-homosexuality Bill is about to pass, I have had many readers express outrage and a desire to tackle the Ugandan Government with protests and petitions. However as I have said all along, this could do more harm than good. If the Bill passes, indeed we will be outraged as an international LGBT community. The Ugandans are fully aware of what the international community thinks about the Bill. However the Ugandan LGBT community is urging caution at this time. While this is a tough course to agree to, as we may feel remiss when the Bill does pass, we owe it to the local groups in Uganda to respect their direction:

**How To Support From A Far About The Recent Resurrection Of The Anti Homosexuality Bill In Uganda**
Released November 13, 2012 at 8:22am ·

Dear Partners, friends and colleagues,

We thank you for all the support you have accorded the Coalition since the tabling of the Anti-Homosexuality Bill in 2009, and we look forward to your continued collaboration in the struggle to see this bill dismissed once and for all.

In response to the recent claims made by the Hon Speaker of the Ugandan Parliament that she would see the Anti-Homosexuality Bill passed before this year comes to a close, we urge you to adhere to the following Action Alert Guidelines and to always seek clarification where there is a difference of opinion on tactics or where there is confusion or need for further information.

We encourage you to:

1. Urgently engage with the leadership of the nation (the President, the Prime Minister, the Leader of Opposition, The Speaker, the Minister for Gender Labor and Social Development, the Minister of Foreign Affairs, the Minister of Ethics and Integrity, the Minister of Health, the Minister of Justice and any other Cabinet Ministers that you can engage with, the Inspector General of Police and the Principal Judge) to impress upon them the needlessness and imminent harm of this bill. This must however been done diplomatically and off the media. There should not be any media/public admonitions PLEASE!
2. Engage with any non-LGBTI partner organizations in Uganda that you may collaborate with or whom you fund to establish what their thinking is on the Anti-Homosexuality Bill, as well as their thinking on other related legislative moves such as the proposal to amend the Penal Code in line with the proposed Anti-Homosexuality Bill. We would strongly encourage other mainstream Ugandan organizations such as human rights NGOs and entities like the Uganda Law Society to speak out strongly against the impartiality of the speaker as well as this draconian bill.
3. Draw international public attention to issues such as corruption (tagging it to the recent corruption cases in the Ministry of Public Service and the Office of the Prime Minister), human trafficking, nodding disease in northern, land-grabbing, as well as the suppression of media freedom and civil society space, so that attention shifts to where it properly belongs; in the best interests of the country’s population as a whole.
4. Go ahead with any preparations of statements, campaigns, and other public documents for when the bill appears on the Order Paper of Parliament (you will be alerted when this happens) as well as for a worst-case scenario in which the Bill is passed into law.

5. Contribute physical, financial, or technical support to the LGBTI community as well as the exposed Human Rights Defenders working with LGBTI rights who are likely to begin to be arrested and charged almost as soon as the Bill is passed. The entire leadership of the Uganda Coalition has decided that any such assistance shall be channeled through a central point at the CSCHRCL secretariat from where it shall be communally managed.

6. Engage with your policy makers to take stronger measures to ensure that LGBTI issues are mainstreamed into calls for proposals, grant agreements, project design, implementation and evaluation as part of a long term strategy to establish LGBTI friendly services and programmes for all Ugandans as an inclusive practice.

**We urge that you do NOT:**

1. **DO NOT** Put out any public press statements on the Bill for now. But you can express your opinion if asked about the Bill. However this opinion must be candid and practical without being ‘insulting’.

2. **DO NOT** Make strong public statements threatening to cut aid or in support of such threats in response to the Anti-Homosexuality Bill, as this can lead to scape-goating of the LGBTI community as well as Human Rights Defenders working with LGBTI rights and whip up sentiments for the Bill. Please note; We would like Ugandans to take charge of this campaign for now. **Only if the Bill is mentioned/programmed in the Business of Parliament or passed into law shall we encourage a fully-fledged international outcry which can come in all forms such as; Public statements (written or spoken), public letters, solidarity campaigns, peaceful protests, interviews, opinion pieces et cetera.**

### SIV and the Expanding Virome

**Monkeys infected with simian immunodeficiency virus have a higher diversity of gut viruses, pointing to a possible role of the virome in SIV pathogenesis**

**By Sabrina Richards | October 11, 2012**

Pathogenic infection with simian immunodeficiency virus (SIV), a relative of HIV that infects non-human primates, is associated with increased diversity of gastrointestinal virus species in rhesus macaques, according to findings published today (October 11) in *Cell*. Though previous work has implicated intestinal bacteria in stimulating chronic inflammation, which is believed to promote progression from HIV or SIV infection to AIDS, the new findings suggest that gut viruses may also play a role.

“This elegant study takes [the role of the gut microbiome] to another level, suggesting the idea that these viruses could be opportunistic infections in the gut of these monkeys,” said microbiologist Donald Sodora, at the Seattle Biomedical Research Institute, who did not participate in the study. In turn, the immune response caused by these viral infections could then fuel the progression of SIV to AIDS.

Some monkey species can be infected with SIV without acquiring full-blown AIDS, while others routinely contract the disease. One difference between these primates appears to be their immune response, with those that develop AIDS showing signs of immune hyperactivation, such as higher levels of inflammatory chemokines and cytokines and activated T cells. This suggests that such excessive inflammation is an important factor in progression to AIDS, possibly because it increases the number of cells vulnerable to HIV and SIV infection. These viruses “love to infect activated CD4 T cells,” which are generated by this immune hyperactivation, explained Sodora. Opportunistic infections that arise as immunocompetence fades are thought to then perpetuate the cycle of immune activation that supports continued and worsening SIV or HIV infection.

Previous work has investigated the influence of gut bacteria in exacerbating inflammation and promoting AIDS, but the role of viruses have been relatively understudied, said immunologist Larissa Thackray of the Washington University School of Medicine. The gastrointestinal viromes of the species generally used as SIV models—rhesus macaques, sooty mangabees, and African green monkeys—are not well described in healthy animals, let alone immunocompromised individuals, she added.

In order to examine the virome of pathogenic and non-pathogenic SIV infections, Thackray and her colleagues turned to rhesus macaques, which succumb to AIDS as a result of SIV infection, and African green monkeys, which regularly resist the disease. Using next-generation RNA and DNA sequencing, the team searched for viral sequences in the guts of both infected and non-infected monkeys, and found that SIV-infected rhesus macaques, some of which succumbed to AIDS during the study, showed an expanded
repertoire of gastrointestinal viruses. SIV-infected green monkeys, which remained healthy, and all uninfected animals showed no viral changes. The results point to the importance of virome composition in inflammation and the progression to AIDS.

However, the new data do not show whether carrying SIV leads to new viral infections, or whether immunosuppression as a result of being SIV-infected allows viruses previously present at undetectable levels to replicate to high levels, acknowledged Thackray. Thus, it’s not yet clear whether the viruses are triggering chronic immune system activation and thereby promoting pathogenesis, or merely taking advantage of a compromised immune system. Future research should probe these possibilities, as well as test human patients to see if HIV infection also correlates with virome changes.

The research also uncovered more than 30 previously undescribed virus species—and this is probably an underestimation. Some types of viruses were so diverse that “we just stopped counting,” said Thackray. Pathologist Guido Silvestri at Emory University, who was not involved in the study, is excited by the number of newly identified species. “In terms of viruses, we’re just scratching the surface, because they’re difficult to isolate with conventional methods,” he said. “We thought most viruses are pathogenic, but that’s probably just a small minority.” Using new sequencing technologies, scientists “are finding viruses everywhere,” he added.

These same advancing technologies will also allow researchers to better discern the role of viruses in the progression of SIV, and possibly HIV, to AIDS, noted Thackray. These new methods “will give the power to tease out some relationship of components of the metagenome.”


Metabolomics Sheds Light on TB Drug
Understanding the mechanism of a classic tuberculosis treatment could refine future strategies for TB drug development.
By Sabrina Richards | November 1, 2012
NIAID
Drugs that interfere with the synthesis of the essential nutrient folate are among the oldest antibiotics around. Now, after decades of successful use, researchers are using metabolomics to discover how, exactly, they work.

One such drug, commonly used to treat tuberculosis (TB), is processed by a key enzyme in folate biosynthesis, breaking down into different products that interfere with enzymes that act later in the pathway. The results, published today (November 1) in Science, contradict the previous belief that the drug, para-aminosalicylic acid (PAS), worked by simply binding the enzyme such that it was not available to process a folate precursor, and may point to novel TB drug targets and antimicrobial strategies beyond enzyme inhibition.

“It’s a really good example of how we don’t really understand how many drugs work,” said Eric Rubin, a tuberculosis researcher at Harvard University who did not participate in the research. “We often operate under the simple assumption that drugs inhibit a process—but as we learn more, it gets more complicated.”

Multiple drug-resistant tuberculosis is a growing problem worldwide—but the search for new drugs is a long and difficult process. “Thus every effort to make maximal use of TB drugs already tried and tested must be made,” Aliimuddin Zumla, a microbiologist at University College London, who did not participate in the study, wrote in an email to The Scientist. The findings that PAS, a time-tested therapeutic, works not by efficiently inhibiting its target enzyme, but by being processed into metabolites that block later steps in folate synthesis, suggests that “rather than inhibition, [the process of] catalysis should be exploited for drug development,” Zumla added.

Interfering with folate synthesis—a key precursor in DNA base synthesis—is a time-tested antibiotic strategy. It has proven effective in humans because, unlike bacteria, people get folate from their diets, and thus have no folate-synthesizing pathways to disrupt, explained Stephen White, a structural biologist at St. Jude Children’s Research Hospital in Memphis, who was not involved with the study.

Sulfa drugs, a class of antibiotics developed in the 1930s, work well against many bacterial species by mimicking para-aminobenzoic acid (PABA), a precursor to folate, inhibiting the enzyme that processes PABA by competing with it for binding. PAS, first used against tuberculosis in 1948, also mimics PABA, but inhibits the enzyme weakly. Oddly, sulfa drugs work poorly against M. tuberculosis, while PAS effectively prevents bacterial growth.

In order to understand more about how PAS and sulfa drugs are processed by M. tuberculosis, Kyu Rhee and his colleagues at Weill Cornell Medical College turned to metabolomics. They treated...
tuberculosis bacteria in culture with each drug individually and measured changes in the bacteria’s metabolites, finding that sulfa drugs were being transformed into inactive derivatives that could not bind to the PABA-processing enzyme, leaving the enzyme free to carry out its folate-synthesis duties.

Scientists had previously speculated that sulfa drugs fail to work against *M. tuberculosis* because they cannot enter the bacteria, but the findings show that the sulfa drugs “get in fine, but they get processed and deactivated,” explained White.

Rhee’s group discovered that PAS, on the other hand, bound to and was processed by the enzyme, breaking down into several different methylated products of PAS, one of which is known to have notable anti-bacterial activity. Other PAS byproducts appear to affect the folate synthesis pathway. Together, the results suggest that PAS is converted by its target enzymes into anti-bacterial products that inhibit bacterial growth through multiple mechanisms, explaining its success over the ineffective sulfa drugs.

“It’s counterintuitive,” said Rubin, that *M. tuberculosis* is most affected not by PAS’s direct binding of a PABA-processing enzyme—which produces inhibition that is too weak to effectively fight bacterial growth—but by the PAS derivatives that are produced as a result of that enzymatic interaction.

The study suggests that researchers may need to tweak their approach, Rubin said. Finding drugs that are broken down into toxic compounds, rather than those that directly inhibit key enzymes, could be an effective approach in the future.

Furthermore, Rhee’s work shows that downstream targets in the folate pathway could also prove to be effective TB drug targets, said White. Identifying which enzymes are targeted by PAS’s metabolites could help researchers identify those targets likely to be most effective. By optimizing how those PAS derivatives poison the folate pathway, researchers may be able to make “PAS a better drug,” White said.


**Cells infected with vaccinia virus (green) lose their cell-cell contacts and disrupt cell layers**

By *The Scientist* Staff | November 5, 2012

![Image of cells infected with vaccinia virus](Image)
A Guide to the Epigenome
Making sense of the data deluge
By Jeffrey M. Perkel | November 1, 2012

Next-Gen Browser: The WashU Epigenome Browser, showing epigenetic data “tracks” in red and long-range chromatin interaction tracks as purple arcs. The tracks are sortable in the heatmap at right.COURTESY OF WASHINGTON UNIVERSITY IN ST. LOUIS

September was a monumental month for genome aficionados. The National Human Genome Research Institute (NHGRI)—funded Encyclopedia of DNA Elements (ENCODE) Project released 30 papers in the pages of Nature, Genome Biology, Genome Research, plus another nine in Science, Cell, and the Journal of Biological Chemistry detailing functional features across the human genome. In all, ENCODE researchers performed nearly 1,650 experiments on 147 cell lines assessing transcription, transcription factor binding, chromatin topology, histone modifications, DNA methylation, and more.

The term that encompasses such myriad functional elements is epigenomics, and researchers are now well aware of the importance of such features in development and disease. So much so, in fact, that in 2008, five years after NHGRI launched ENCODE, the NIH funded a second large-scale mapping project. The NIH Roadmap Epigenomics Program had compiled some 61 “complete” epigenomes (genome-wide epigenetic profiles of a variety of cell types) as of May 2012, with more scheduled for inclusion in the project’s upcoming release number 8 of the Human Epigenome Atlas.

There’s a lot researchers can do with these data sets. In an early demonstration, The University of Washington’s John Stamatoyannopoulos, a member of both the ENCODE and Roadmap consortia, and colleagues mined these data to address the puzzling fact that the vast majority of trait- and disease-associated sequence variants (SNPs) identified in genome-wide scans lie outside of any protein-coding sequence. By correlating those variant positions against accessible chromatin regions identified in the two epigenomics projects, Stamatoyannopoulos and his team found these variants often overlap with regulatory elements. They then identified the genes upon which those regulatory elements might act—some located hundreds of thousands of bases away (Science, 337:1190-95, 2012).

Both projects have made their data freely available to the research community, many of whom may want to see what these data sets have to say about their own particular gene, tissue, or pathway of interest. Yet for many researchers, handling, parsing, and visualizing so much information can be intimidating. The ENCODE data set alone weighs in at 15 terabytes.

The best advice, says John Satterlee, a Health Scientist Administrator at the National Institute on Drug Abuse and a co-coordinator of the NIH Roadmap Epigenomics Program, is just to jump in and see what’s there. “It’s not like you’re wasting reagents—this is just an in silico experiment,” he says.
We asked Satterlee and fellow experts to show us how to make use of these visualization tools. Here is what they said.

Where Can I Find The Data?

ENCODE project data are available at encodeproject.org, and may be visualized in the University of California, Santa Cruz (UCSC) genome browser (genome.ucsc.edu) by activating ENCODE data tracks in the track selection area (these are demarcated with an NHGRI “helix” icon).

You can view and/or download Roadmap Epigenome data sets from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (www.ncbi.nlm.nih.gov/geo/roadmap/epigenomics), or view them as a remote “Track Hub” at the UCSC genome browser or one of several, generally faster, UCSC mirrors (e.g., www.epigenomebrowser.org). Other Roadmap visualization sites include the Human Epigenome Atlas (www.genboree.org/epigenomeatlas), hosted at the project’s data coordination site at Baylor College of Medicine; the Roadmap Epigenomics Data Browser (www.roadmapepigenomics.org/data); and the NCBI Epigenomics Browser (www.ncbi.nlm.nih.gov/epigenomics).

For something completely different, Washington University in St. Louis hosts a “next-gen” browser at epigenomegateway.wustl.edu (Nat Meth, 8:989-90, 2011). The WashU Epigencode Browser lets users explore the human epigenome by clicking the metadata heatmap at the right of the browser. The browser also recently added a nifty “long-range interaction tracks” feature, which allows users to view ENCODE project chromatin-interaction data produced by such techniques as 5C, HiC, and ChIAPET. These appear as “arcs” beneath the genome tracks, linking distal, but physically connected, chromosomal regions.

How Do I Search Data Sets?

Both ENCODE and the NIH Roadmap Epigenomics Project provide data matrices so users can browse data sets by cell or tissue type, or by epigenetic mark. “You can select along at least three dimensions,” explains Aleksandar Milosavljevic, a geneticist at Baylor College of Medicine. “One can select sample types, assays, and genomic coordinates.”

Suppose, for instance, that you are interested in H1 human embryonic stem cells. From the ENCODE project home page, select “Experiment Matrix” in the navigation bar on the left side of the page; the resulting clickable table shows you that the project has produced 124 data sets, including 10 RNA-seq and 91 ChIP-seq analyses, for H1-hESC cells. Clicking any box in the matrix allows you to view those particular data in the UCSC genome browser.

Roadmap Epigenomics data matrices are available on the Human Epigenome Atlas and Roadmap Epigenomics Data Browser. Use the search windows on both sites to filter by tissue type as needed. Alternatively, users can scan tissue types visually by selecting one of three options (Embryonic Stem Cells, Fetal Tissues, or Adult Cells & Tissues) under the Visual Data Browser heading at the top of the Roadmap Epigenomics Data Browser. This project collected 106 H1 embryonic stem cell data sets, according to the Atlas, and you can scan them all for your gene or genes of interest, if you wish.

How Do I Find The Epigenetic State Of My Gene?

All genomic and epigenomic browsers allow users to view specific genomic locations. UCSC browser users can specify a given gene (say BRCA1) or genomic locus in the search window at the top of the browser page. The data are presented as graphs of signal intensity vs. genomic position, and like all UCSC browser tracks, may be turned on or off and moved up or down to simplify visualization.

In the WashU Epigencode Browser, after selecting your genome of interest (human, mouse, Drosophila, and more), you can view specific genomic locations by clicking Apps > Relocation in the browser’s floating window. To view all genes in a given pathway at once, scroll to the vertical menu at the bottom of the browser window and select Genomic View > Gene Set View > KEGG Pathways (or, for unrelated genes, Custom Gene Set). For instance, try “path:hsa03420,” the nucleotide excision repair pathway. The resulting view shows you 68 genes from that pathway side by side, even though they are located on different chromosomes.

This particular browser’s view is highly configurable; try right-clicking on individual data tracks in the genome heatmap to change each row’s appearance. Or, sort by metadata, such as epigenetic mark or cell type, by clicking the metadata heatmap at the right of the browser. The browser also recently added a nifty “long-range interaction tracks” feature, which allows users to view ENCODE project chromatin-interaction data produced by such techniques as 5C, HiC, and ChIAPET. These appear as “arcs” beneath the genome tracks, linking distal, but physically connected, chromosomal regions.

“There has been quite a bit of technology development in assays to profile chromatin interaction . . . but no good ways to visualize [those interactions] on a linear genome browser,” Wang explains.
If you’re interested only in the epigenetic state of specific genes in isolation, you can also view them outside of a genome browser. From the Human Epigenome Atlas home page, link to the current release to access the data matrix page, then select the boxes corresponding to the data sets of interest. Select the six MeDIP-Seq and MRE-Seq data sets (methylation and lack of methylation, respectively) for Breast Luminal Epithelial Cells, Breast Myoepithelial Cells, and Breast Stem Cells. At the top of the window, click Selections > View In > Atlas Gene Browser.

In the page that comes up, type BRCA1 in the Gene search box. The page will display bar graphs of average methylation intensity across each of the gene’s 23 exons, introns, and its promoter. You can select additional genes by clicking Add Gene (e.g., BRCA2), or add genes from the same pathway by clicking the Pathway Browser button (three red circles arranged in a triangle).

How Can I Get A Bird’s-Eye View Of The Epigenome?
In the WashU browser, right-click on any data track in the genome heatmap and select Genome Snapshot; the resulting pop-up maps that particular data set across all 23 human chromosomes, allowing you to zoom in on points of interest. From this view you can see that trimethylation of lysine-9 on histone H3 (H3K9me3) is highly enriched (i.e., there are sharp signal peaks) around each centromere in the HUES6 human embryonic stem cell line.

If you’re looking for genes that differ, epigenetically speaking, between two cell types or conditions, try the NCBI Epigenomics Browser’s “Compare Samples” tool. It highlights the most epigenetically different genes in any two data sets—a good way to identify genes that might be differentially regulated. Comparing lysine-27 trimethylation on histone H3 (H3K27me3) in human fibroblasts and human embryonic stem cells, for instance, flags 20 genes with variable levels of distinctiveness.

How Do I Compare My Own Data To The Public Data Sets?
Say you’ve already mapped H3K27me3 across your gene of interest. You can overlay those data on the ENCODE or Roadmap data sets. The easiest option, says Lisa Chadwick of the National Institute of Environmental Health Sciences (NIEHS), one of the Epigenomics Roadmap’s program directors, is uploading a custom data track of those data to the UCSC genome browser. From the browser home page, select Genome Browser at the top of the left navigation bar, then in the search box select Add Custom Tracks. Your data must be properly formatted for display, for instance, as bigBed or bigWig files. (See the UCSC genome browser User Guide for more information.)
Heart Of The Data: The Roadmap Epigenomics Project visual data browser filters data sets by adult, fetal, or embryonic tissues or cell types.COURTESY OF ROADMAP EPIGENOMICS PROJECTThe WashU Epigenome Browser also supports custom tracks. Scroll to the bottom of the window, and select Tracks > Custom Track. Users can also batch upload multiple tracks, creating what’s called a “data hub,” says Wang.

Where Can I Go For More Information?
The epigenome projects presented massive data visualization problems, Chadwick says, simply by virtue of the size of the data sets—not to mention the fundamental complexity of the data themselves. “That’s why we ended up with all these different sites and all these different ways to look at [the data],” she says, “because there’s no one way to do it.”

Because each site is a bit different, the only way to see what they can do is to try them out. Help is available, however. There is a video tutorial on working with ENCODE data in the UCSC browser, at www.openhelix.com/ENCODE/. WashU has produced several video tutorials on its next-gen browser, too, available at epigenomegateway.wustl.edu.

For more hands-on help, Baylor College of Medicine organizes workshops, each with up to 40 participants, which focus on its epigenomics tools and provide FAQs and Use Cases to walk researchers through some common data-analysis problems. According to Milosavljevic, these workshops center around Genboree Workbench (Genboree.org), a Baylor-built framework that integrates epigenomics and genomics software tools with epigenomic and omics data sets, such as transcriptome and genome data. “Our goal as a data coordination center is not only to deliver these reference data sets but also to enable disease projects and basic science projects to probe these data sets using an integrated suite of tools and perform analyses that combine their own private data with public reference data sets,” Milosavljevic says.

The last of three 2012 Epigenome Informatics workshops was held in early October, with more scheduled for 2013, says Milosavljevic. For those who cannot wait that long, Chadwick, a program administrator in NIEHS’s Division of Extramural Research & Training, along with NHGRI staff representing the ENCODE consortium, will be holding a satellite workshop on November 8 at this year’s American Society of Human Genetics annual meeting in San Francisco.
“It’s just going to be a couple of hours where we’re going to be talking about, from a human genetics perspective, how this kind of data could be useful to you, and where you can find the data,” Chadwick says.

Given the complexity of the epigenome data sets, and their potential value, that sounds like time well spent.

**Detecting Biothreats, Faster and Cheaper**

A new technique simplifies and accelerates the development of tests for identifying potential biological weapons.

By Ed Yong | November 5, 2012

Scientists at the Texas Biomedical Research Institute (TBRI) have created a fast and efficient way of developing tests for potential bioterror agents. The technique, published today (November 5) in *Scientific Reports*, quickly identifies antibodies that recognize bacterial toxins or viral proteins in a few days, using simple equipment found in most facilities around the world.

This technique is “more suitable for resource limited laboratories” than traditional methods that require expensive equipment like chromatography systems, said Kim Janda, a chemist from the Scripps Research Institute, who was not involved in the study. “I think it will find ample use in other laboratories in the future.”

Currently, to find antibodies that recognize potential biological threats—a key step towards developing effective diagnostics—scientists start with a large panel of possible antibodies, and gradually isolate those that recognize a given target. It is a laborious process—each round of screening can identify hundreds of antibodies, which have to be individually purified using large cultures and expensive equipment like chromatography systems. The whole process can take months.

“I was faced with this dilemma of deconvoluting hundreds of antibodies, and didn’t want to spend a year purifying the darn things,” said TBRI’s Andrew Hayhurst, who studies ways to detect biothreats.

So, together with TBRI colleague Laura Sherwood, he devised a solution. He starts by making extracts from different strains of *E. coli*, each engineered to produce a slightly different antibody. Each extract is loaded into a separate well on a large plate. The antibodies all have a molecule called biotin on their tail, which binds tightly to neutravidin, a protein that coats the wells.

Then, Hayhurst adds the target. It sticks to some of the immobilized antibodies, but not others. He adds another round of antibodies that bind to the immobilized targets. Finally, he applies another batch of neutravidin that sticks to the second layer of antibodies, this time labeled with a tag that can be made visible to the naked eye, such as a fluorescence marker. He rinses the plate to remove any loose tags, and simply looks for which wells are producing the right color, indicating the antibodies in that well successfully recognized the microbial target.

Hayhurst and Sherwood used their method to identify pairs of antibodies against two potential bioterror weapons—botulinum toxin, one of the most potent known bacterial poisons, and Ebola virus. By rapidly finding antibodies that bind to such target, scientists could quickly develop tests for them. “It’s an environmental surveillance tool,” said Hayhurst.

The same method could also be used to develop new diagnostic tests for “virtually any target,” Hayhurst said. For the moment, he is focusing on known biothreats, but the technique could eventually be help create a rapid response to an unfamiliar threat used in an attack, he said. “The knowledge gained in targeting the known will be of use in smoothing the path to targeting the unknown.”

The system is incredibly simple, and takes very little equipment. All the *E. coli* strains can be grown in milliliter-sized table-top cultures. “Anyone in the world can just do this on their bench,” said Hayhurst. “It’s so simple, there’s no witchcraft involved. It’s about the cheapest way of doing this possible.”

When the cultures are ready, it takes just an hour to screen hundreds of antibodies at once. The technique immediately focuses an experimenter’s attention on the effective antibodies, bypassing the need to purify them. And once the right antibodies have been identified, Hayhurst can produce them en masse.
using the same engineered E. coli strains. “You can immediately start cranking out milligrams of antibodies,” he said.

“I am extremely excited by these innovations,” said Paul Gulig, a microbiologist from the University of Florida who was not involved in the study. “They streamlined many things.”


**Opinion: Science in the Courtroom**

Should biological explanations for criminal behavior influence a judge’s or jury’s decision about how to handle a case? If so, how?

By James Tabery | November 6, 2012

Scientific evidence concerning the biological causes of bad behavior is becoming increasingly common in the courtroom. Forensic psychiatrists at Vanderbilt University have genetically screened defendants charged with first-degree murder for a gene associated with antisocial personality disorder, for example. And when it came time to sentence convicted murderer Brian Dugan, neuroscientists performed neuroimaging on Dugan's brain in order to claim he has a defective, psychopathic brain.

What would you do if you were faced with such a decision? Imagine you’re a juror tasked with the job of recommending a sentence for a criminal found guilty of aggravated battery. The criminal, Jonathan Donahue, went into a Burger King restaurant with the hope of robbing it, then beat the manager so severely that he sustained brain damage. After he was arrested, Donahue seemed to revel in his crime, even going so far as to have a king’s crown tattooed on his back.

At the sentencing hearing, a psychiatrist provides expert testimony saying that Donahue is a diagnosed psychopath. She explains that psychopathy is a clinical diagnosis defined by impulsivity, lack of empathy, and lack of remorse. The judge tells you that the standard sentence for cases of aggravated battery is about 9 years.

**First Question**: With this information, how many years in prison will you recommend for Donahue?

There’s one more expert witness. This one is a neurobiologist, and he tells you that Donahue has a particular gene that contributes to atypical brain development. Specifically, the part of Donahue's brain that controls his violence-inhibition mechanism is damaged. In normal humans, the violence-inhibition mechanism automatically creates anxiety when they recognize that other humans are in pain or distress. Psychopaths, like Donahue, lack a normal violence-inhibition mechanism.

**Second Question**: In light of this additional neurobiological evidence, how many years in prison will you recommend for Donahue?

How did you answer the Second Question relative to the First Question? If you increased Donahue’s sentence, you probably did so because you interpreted the neurobiological evidence as suggesting his biological constitution makes him a continued threat to society. On the other hand, if you decreased Donahue’s sentence, you probably did so because you interpreted the neurobiological evidence as suggesting his biological constitution makes him less responsible for his actions. Or, you could have dismissed the neurobiological evidence entirely and recommended the exact same sentence.

This is the double-edged sword of the science of criminal behavior. The exact same evidence could either increase or decrease punishment, depending on how that evidence is interpreted.

With scientific evidence about the causes of criminal behavior becoming more and more common in the courtroom, the legal system faces a pressing question: Which way will the double-edged sword cut? In Dugan’s murder case, a jury ultimately sentenced Dugan to death, but according to his attorney the scientific evidence switched a slam dunk case against Dugan into a much more complicated decision for the jurors. To investigate this question in a systematic way, my colleagues and I performed a national experiment involving US state trial court judges. We presented the judges with Donahue's case and asked them to sentence him. The results of this experiment were published last month in Science. The judges told us that on average they sentenced convicts guilty of aggravated battery to about 9 years in prison. The judges who received only expert testimony concerning Donahue's diagnosis of psychopathy sentenced him on average to almost 14 years in prison. But the judges who received the expert testimony concerning Donahue’s diagnosis of psychopathy as well as the evidence concerning the neurobiological causes of his psychopathy sentenced him on average to about 13 years in prison. Compared to just the diagnosis of psychopathy, that is, the neurobiological evidence reduced Donahue’s sentence by roughly a year (a statistically significant difference).
So, our study suggests which way the double-edged sword might cut—towards slightly shorter sentences. But there is another pressing question, one at the intersection of science, philosophy, and the law: Which way should the double-edged sword cut?

The presence of scientific evidence about the causes of criminal behavior is only likely to increase in the courtroom. As a result, scientists and non-scientists alike need to discuss this issue and decide how biological knowledge should influence the legal system.

To get the conversation going, in the Comments section below, list your answers to the First and Second Questions and explain your justification for the increase, decrease, or lack of any change in the prison sentence that you recommended for Donahue.

**James Tabery** is a professor of philosophy at the University of Utah.

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**Comments**

**TallySkeptic**
Posts: 4
November 8, 2012

I would answer "9 years in prison" to both of the author's questions. For me the main purposes of imprisonment are to 1) protect the public for some period of time, 2) serve as a warning to the public about what could happen to anyone who committed the same crime, 3) enable revenge by proxy for the victim, her family, and friends, 4) provide an opportunity for study of the offender, 5) provide an opportunity to "fix" the offender. While the offender is in prison, experts can try to determine what were the causes of the criminal behavior and implement various programs to correct those causes. The sentence of capital punishment, however, should be eliminated.

**Madmacks**
Posts: 1
November 8, 2012

The implications of modifying sentences based on psychopathy is a slippery slope. The modification of the sentence would be based on science's ability to predict his possibility for reform or recidivism, or predicting his future behavior. If Psychopathy is accepted by the Court as grounds for modifying sentencing, then doesn't it also become grounds for predicting the behavior of other litigants before the Court?

The patterns of behavior of psychopaths are uniquely characteristic and evidence of these patterns either exists or does not exist. The condition impacts the lives of the psychopath and the people around them, so its not hard to rule in or out. So, shouldn't psychopathy also be considered by Judges in 'high-conflict' divorces, where one parent is out to punish or destroy the other parent? Psychopathy could also be considered by Judges in cases of fraud, embezzlement or other 'white collar' felonies. Psychopathy is also seen in children as young as 5. Perhaps the Juvenile Courts should do more to screen the 'at-risk' youths for psychopathy.

Based on my experience in Civil Court, Judges do not wish to touch the issue of psychopathy. I have seen psychological experts, lawyers and judges completely ignore undeniable patterns of behavior consistent with psychopathy, in order to avoid having to address the issue in Court.

Psychopathy is a pandora's box for the legal system that it is fighting hard to keep closed.

**ThinkAboutIt**
Posts: 1
November 8, 2012

This is truly distressing to contemplate. The best sentence I can think of is to remand the criminal to an institution where he will be cared for, yet locked away so he will not be a threat to others.

Should there first be the penalty of a jail sentence? This would be discretionary. If the subject is able to understand the difference between right and wrong, he should be held responsible for his actions and meted out the standard punishment, whether he is able to feel his victim's pain or not. Lack or empathy is one thing; ability to understand rules is another.

**Devin Camenares**
Posts: 1
November 8, 2012

At first blush, I would say that the way the sword cuts will reflect what the purpose of detention in prison is.

If placing a criminal in a prison cell is done primarily to punish evil and simply serve justice, then the genetic basis should remove, at most, a slight amount of responsibility. Therefore a reduction in time served would be called for.

If the prison time is intended to remove a harmful criminal from society, and hopefully lead to the rehabilitation of this criminal, then clearly evidence for a partially genetic cause for their actions should led to an extended prison sentence.

The article already points this out, but I would add that the first is more abstract, and the latter is related to more practical concerns. I subscribe to the latter interpretation, since I usually favor the practical over the abstract.

After all, notions of justice, responsibility, and fairness to the criminal (in my opinion) are hard to appreciate when the streets are made more dangerous.

**Francien Verhoeven**
Posts: 1
November 8, 2012

Crime and punishment are actions always committed in relation to society at large. The intent of the law is to keep an ordered society with the aim of working towards a betterment of society for all.

With this in mind, we must consider the criminal and the punishment so given.

Criminal activity is committed under all sorts of circumstances; there is the poor citizen in need of some goods; there is the jealous wife who would prefer the other woman to no longer exist; there is the greedy investment banker who would like to see a different bottom line; there is the psychopath who likes to shatter someone's skull.

All criminal activity is by deviant behaviour expressed in accordance with good societal practices. Why would it make a difference if we can now scan the brain of a psychopath and figure out that the pathways within his or her brain no longer line up
properly? Perhaps a person is poor because some neurons are fired incorrectly. Perhaps a jealous or greedy person has some major misfirings going on within his or her brain also.

Of course, it could be said that the psychopath commits a crime for the sheer excitement of it all, but nonetheless, such is considered a malfunction of the brain in connection to the wider workings of a society at large—such behaviour is impossible to tolerate when working towards the societal betterment for ALL.

Just because scientific methods are easier applied when scanning the brain of a psychopath, presumably because such scan would show obvious malfunctions, that does not mean that the poor person, or the jealous person, or the greedy person does not inhibit some sort of shortcomings vis-a-vis proper societal interactions; low intelligence, jealousy and greed are all shortcomings when considered within the larger picture of proper societal interactions.

Prisons and prison sentences are there for several reasons: to protect society at large from harm’s way; to let the criminal bear the burden of responsibility; and to set precedent.

Prison settings should be as such that the criminal of any kind is helped while being incarcerated. The best help any prison setting can offer is for the criminal to find a corrected sense of self within a structured setting. By means of daily work activities, learning activities and social interactive activities(to mention just a few) the incarcerated criminal may find a corrected sense of self, It could very well be that the psychopath will never find a corrected sense of self no matter how long the prison sentence would be. Such continued psychopathic behaviour would then be considered unworthy of participating within a free and open society, and the psychopath would be locked up for life.

The laws already make a clear distinction between murder one, murder two, manslaughter etc. The same goes for theft—petty theft, robbery etc. And so forth. The law makes distinctions between all sorts of crimes being committed.

It should make no difference whether the psychopath’s brain can show misfirings within the brain since all deviant behaviour is in essence due to the improper understanding of societal well being. And all of our human understandings originate within the functions of the brain.

Therefore no exceptions should be made in any case.

**jttott**

Posts: 2

November 8, 2012

First question: 20 years because he almost killed the guy and left him permanently brain damaged.

Second question: death penalty. A genetically confirmed psychopath has no chance of rehabilitation and will end up killing people.

**Hugh-F-61**

Posts: 8

November 12, 2012

The first info describes the symptoms, the effect, the second the cause. They say the same thing, he is incurable. Sentence: the same, lifetime confinement in a hospital for the dangerously insane, for the protection of others. I would not want to be responsible for the life he destroys if he is ever released.

**Roy Niles**

Posts: 4

November 16, 2012

The less responsible you are for your actions, the more time, perhaps, you should be segregated from a self regulated society and placed under other regulated supervision. But of course we aren’t philosophically prepared to do that.

We have an adversarial justice system in the US which in the end requires each side’s representatives to lie for justice. Responsibility becomes only incidental to the question of who wins the liars contest.

**Ebola from Pigs to Monkeys**

A deadly Ebola virus can spread from pigs to monkeys without direct contact, pointing to pig farms as a possible contributor to outbreaks.

By Ed Yong | November 15, 2012

Ebola viruses can cause fatal disease in humans and other primates, pigs can carry the infections with few ill effects. Now, Canadian scientists have shown that apparently healthy pigs can pass the deadliest species of Ebola to monkeys, even without ever coming into contact with them.

The study, published today (November 15) in *Scientific Reports*, marks the first time that the virus has spread between different species in a lab experiment, and suggests that pig farms could be facilitate such species-hopping in more natural conditions.

However, Gary Kobinger from the University of Manitoba, who led the study, cautioned that “we still don’t know if pigs are playing any role in the natural transmission or ecology of Ebola virus in Africa.”

“An epidemiological survey of wild and domestic pigs in sub-Saharan Africa is now necessary,” agreed Shigeru Morikawa from the National Institute of Infectious Diseases, Japan, who was not involved in the research.

Ebola has been found in gorillas, chimps, duikers (a small antelope), humans, and recently, pigs. The identity of its reservoir species is unclear, although bats are the most likely candidate. Until recently, no one even knew that pigs could carry Ebola. But in 2009, Roger Barrette found the Reston Ebola virus—the only one of five Ebola species of that does not seem to cause disease in humans—among Philippine pigs and antibodies against it among six pig farmers. More worryingly, Kobinger’s team also showed that Zaire-Ebola virus—the deadliest of the five, with a fatality rate of up to 90 percent in humans—can also infect pigs and spread between them through direct contact.
“Pigs are remarkably versatile animals when it comes to acquiring and transmitting infections,” said Tara Smith from the University of Iowa, who studies emerging infectious diseases and was not involved in this study. “They have been implicated in the spread of a variety of nasty zoonotic viruses: influenzas, Nipah virus, possibly Hendra virus, and now at least two types of Ebola.”

In pigs, Ebola mainly infects the lungs and airways, which makes them well-suited to spreading the virus through the air. To see if this was possible, Kobinger teamed up with Hana Weingartl from the University of Manitoba. They used nose swabs to infect piglets with Zaire Ebola, then placed them in a room with four cynomolgus macaques. The monkeys lived inside a wire cage within the pig pen, so the two species never made direct contact despite sharing living quarters.

The piglets developed heavier breathing and mild fevers, but were otherwise unharmed by the infection. But the monkeys were not as lucky. After 2 weeks, the pigs had passed the virus to all their neighboring macaques, who developed bloody spots on their chest and limbs and signs of damage in their lungs.

The study shows that the virus can spread without direct contact, but “keep in mind that Ebola is not suddenly an airborne virus, like influenza,” said Kobinger. Instead, the virus could have jumped from pigs to monkeys via small droplets in the air, or larger ones that splashed into the monkeys’ cages when the handlers cleaned the floor of the pigs’ area.

Indeed, the local nature of all known outbreaks suggests that it does not disperse effectively like an airborne virus would. Furthermore, it’s still unclear how common indirect transmission between species is in the real world. It could explain why some Philippine pig farmers were infected with Reston Ebola even though they were not involved in slaughtering the swine, and had not come into contact with contaminated tissues, Kobinger noted. But, he added, “this work was done in controlled conditions, and may not be representative of pigs running outside in the field,” said Kobinger. His team is now headed to Africa, to collect samples from pigs in areas that have had Ebola outbreaks in the past. “We just started this and are looking forward to see the results.”


**Personality Predicts Placebo Effect**

People with certain personality traits are more likely to get pain relief from a placebo, a finding that could help improve clinical trials

By Dan Cossins | November 16, 2012

Individuals who are altruistic, resilient, and straightforward show greater activity in brain regions associated with reward and are more likely to enjoy pain relief when a placebo is administered during a painful experience, according to a study reported this week (November 15) in *Neuropsychopharmacology*. The findings suggest that simple personality tests could be used to improve the accuracy of clinical trials by identifying people likely to skew results with high placebo responses.

“This is interesting because it’s one of the first studies to look at how personality traits are associated with placebo analgesia not only in terms of subjective reports of pain relief, but also with quite solid objective measures in key parts of the brain,” said Tor Wager, a neuroscientist at the University of Boulder, Colorado, who was not involved in the study.

Placebos are known to have strong analgesic effects. In 2007, neuroscientist Jon-Kar Zubiena of the University of Michigan showed that such effects were associated with activity in the nucleus accumbens, a brain region involved in reward and pleasure. That suggested that placebo analgesia might occur in part because positive expectations of reward (pain relief) spike dopamine levels in the brain and stimulate the release of endogenous painkillers called mu-opioids.

But individuals vary considerably in their responses, and some studies have suggested that personality traits such as optimism and anxiety may predict response levels. Others have found that a composite of personality traits—including novelty seeking, harm avoidance, fun seeking, and reward
responsiveness, which are thought to be related to dopamine reward circuits—can predict a substantial portion of placebo analgesic effects. Still, “there was nothing terribly conclusive,” said Zubieta.

To better understand how personality is associated with placebo analgesia, Zubieta and his colleagues assessed the personality traits of 47 healthy volunteers. Then they asked each volunteer to lie in a positron emission tomography (PET) scanner for the duration of a standard pain challenge. First, painless isotonic saline was injected into the jaw muscle and, 20 minutes later, a pain-inducing hypotonic injection. Volunteers were told about these two conditions but not the order in which they would occur, allowing for expectation of pain in both conditions. The conditions were then repeated for another scan session but this time the volunteers were given a placebo consisting of intravenous infusions of isotonic saline every 4 minutes, which they were told would reduce pain.

The PET scan recorded the activation of endogenous opioid receptors in the brain, and blood samples were taken every 10 minutes to measure placebo-induced changes in the stress hormone cortisol. Meanwhile, the volunteers were also asked to rate the intensity of the pain they felt every 15 seconds. The researchers observed significant reductions in pain intensity ratings in response to placebo, but found that expectation of analgesia—measured by asking the volunteers during the pain challenge—was not significantly correlated with response, suggesting that positive expectations alone are not enough for a placebo-induced pain response.

But they also found that people with certain personality traits—specifically, those who scored high on resiliency, altruism, and straightforwardness, and low on measures of “angry hostility”—were more likely to experience a placebo-induced painkilling response. Importantly, such individuals also had decreased cortisol levels and greater activation of endogenous opioid receptors in brain regions associated with reward.

“We were able to link some personality traits with analgesia response at the level of brain chemistry,” said Zubieta, as well as subjective feelings. In fact, statistical analyses showed that a composite of these four traits accounted for 25 percent of the variance in subjectively reported placebo analgesic responses, and for 27 percent of the variance observed in objective measures like the activation of endogenous opioid receptors.

“Studies like this are giving us a new set of candidate personality measures that can predict for placebo analgesia, and they’re mostly positive traits,” said Wager. “So placebo responders are being cast in a much more positive light, personality-wise, than they were a few decades ago, when they were thought to be hysterical and neurotic.”

If replicated with larger sample sizes, the results suggest that these new measures could also help to improve the accuracy of clinical trials, Zubieta added. “One big difficulty is trying to control for people with very high placebo response,” he said. “Many trials fail not because the compound doesn’t work, but because placebos are also effective, which creates noise.” By using personality measures to stratify those more likely to exhibit a placebo effect and incorporate the likelihood of a placebo response into the data analyses, researchers may be able to more effectively identify a drug’s true effect, Zubieta said.


How Bacteria Inactivate Immune Defenses

ScienceDaily (Nov. 15, 2012) — A new study by researchers at Imperial College London has identified a way in which Salmonella bacteria, which cause gastroenteritis and typhoid fever, counteract the defence mechanisms of human cells.

One way in which our cells fight off infections is by engulfing the smaller bacterial cells and then attacking them with toxic enzymes contained in small packets called lysosomes.

Published November 15 in Science, the study has shown that Salmonella protects itself from this attack by depleting the supply of toxic enzymes.

Lysosomes constantly need to be replenished with fresh enzymes that are generated from a Salmonella bacteria (green) invade a red blood cell. (Credit: Professor David Holden, Imperial College London)
factory within our cells. These enzymes are carried from the factory along a dedicated transport pathway. After dropping off new enzymes at lysosomes, the transport carriers are sent back to the factory to pick up new enzymes.

In the study, led by Professor David Holden from the Department of Medicine and MRC Centre for Molecular Bacteriology and Infection, the group discovered that *Salmonella* has developed a specific way to interfere with the system that restocks the lysosomes with enzymes. They found that after bacteria have been engulfed by the cell, but before they are killed, *Salmonella* injects a protein that prevents the cell from recycling the transport carriers between the factory and the lysosome.

This means that *Salmonella* effectively cuts off the supply line of the enzymes that would otherwise kill it. As a result, the enzymes get re-routed out of the cell and the lysosomes lose their potency. *Salmonella* is then able to exploit the disarmed lysosomes by feeding off the nutrients they contain.

Professor Holden said: "This seems to be a very effective way for these harmful bacteria to interfere with our cell's defence mechanisms, and then exploit the defective lysosomes to their own benefit."

"Our challenge now is to understand in greater detail how the injected *Salmonella* protein works at the molecular level, and—potentially—to exploit our findings to develop more effective vaccines. This is especially important since many *Salmonella* strains are now resistant to antibiotics."

Different strains of *Salmonella* cause gastroenteritis, blood infections and typhoid fever, which together are responsible for millions of human illnesses and deaths each year. The research project was funded with grants from the Medical Research Council and the Wellcome Trust.

**Journal Reference:**

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**New Way for Antibiotic Resistance to Spread**

ScienceDaily (Nov. 15, 2012) — Washington State University researchers have found an unlikely recipe for antibiotic resistant bacteria: Mix cow dung and soil, and add urine infused with metabolized antibiotic. The urine will kill off normal *E. coli* in the dung-soil mixture. But antibiotic-resistant *E. coli* will survive in the soil to recolonize in a cow's gut through pasture, forage or bedding.

"I was surprised at how well this works, but it was not a surprise that it could be happening," says Doug Call, a molecular epidemiologist in WSU’s Paul G. Allen School for Global Animal Health. Call led the research with an immunology and infectious disease Ph.D. student, Murugan Subbiah, now a post-doctoral researcher at Texas A & M. Their study appears in a recent issue of the online journal PLOS ONE.

While antibiotics have dramatically reduced infections in the past 70 years, their widespread and often indiscriminate use has led to the natural selection of drug-resistant microbes. People infected with the organisms have a harder time getting well, with longer hospital stays and a greater likelihood of death. Animals are a major source of resistant bugs, receiving the bulk of antibiotics sold in the U.S.

The scientists focused on the antibiotic ceftiofur, a cephalosporin believed to be helping drive the proliferation of resistance in bacteria like *Salmonella* and *E. coli*. Ceftiofur has little impact on gut bacteria, says Call.

"Given that about 70 percent of the drug is excreted in the urine, this was about the only pathway through which it could exert such a large effect on bacterial populations that can reside in both the gut and the environment," he says.

Until now, conventional thinking held that antibiotic resistance is developed inside the animal, Call says.

"If our work turns out to be broadly applicable, it means that selection for resistance to important drugs like ceftiofur occurs mostly outside of the animals," he says. "This in turn means that it may be possible to develop engineered solutions to interrupt this process. In doing so we would limit the likelihood that antibiotic resistant bacteria will get back to the animals and thereby have a new approach to preserve the utility of these important drugs."

One possible solution would be to find a way to isolate and dispose of residual antibiotic after it is excreted from an animal but before it interacts with soil bacteria.

The WSU experiments were performed in labs using materials from dairy calves. Researchers must now see if the same phenomenon takes place in actual food-animal production systems.

**Journal Reference:**
Breakthrough nanoparticle halts multiple sclerosis ***

New nanotechnology can be used for Type 1 diabetes, food allergies and asthma

- New nanoparticle tricks and resets immune system in mice with MS
- First MS approach that doesn’t suppress immune system
- Clinical trial for MS patients shows why nanoparticle is best option
- Nanoparticle now being tested in Type 1 diabetes and asthma

CHICAGO — In a breakthrough for nanotechnology and multiple sclerosis, a biodegradable nanoparticle turns out to be the perfect vehicle to stealthily deliver an antigen that tricks the immune system into stopping its attack on myelin and halt a model of relapsing remitting multiple sclerosis (MS) in mice, according to new Northwestern Medicine research.

The new nanotechnology also can be applied to a variety of immune-mediated diseases including Type 1 diabetes, food allergies and airway allergies such as asthma.

In MS, the immune system attacks the myelin membrane that insulates nerves cells in the brain, spinal cord and optic nerve. When the insulation is destroyed, electrical signals can’t be effectively conducted, resulting in symptoms that range from mild limb numbness to paralysis or blindness. About 80 percent of MS patients are diagnosed with the relapsing remitting form of the disease.

The Northwestern nanotechnology does not suppress the entire immune system as do current therapies for MS, which make patients more susceptible to everyday infections and higher rates of cancer. Rather, when the nanoparticles are attached to myelin antigens and injected into the mice, the immune system is reset to normal. The immune system stops recognizing myelin as an alien invader and halts its attack on it.

"This is a highly significant breakthrough in translational immunotherapy," said Stephen Miller, a corresponding author of the study and the Judy Gugenheim Research Professor of Microbiology-Immunology at Northwestern University Feinberg School of Medicine. "The beauty of this new technology is it can be used in many immune-related diseases. We simply change the antigen that’s delivered."

"The holy grail is to develop a therapy that is specific to the pathological immune response, in this case the body attacking myelin," Miller added. "Our approach resets the immune system so it no longer attacks myelin but leaves the function of the normal immune system intact."

The nanoparticle, made from an easily produced and already FDA-approved substance, was developed by Lonnie Shea, professor of chemical and biological engineering at Northwestern’s McCormick School of Engineering and Applied Science.

"This is a major breakthrough in nanotechnology, showing you can use it to regulate the immune system," said Shea, also a corresponding author. The paper will be published Nov. 18 in the journal Nature Biotechnology.

Miller and Shea are also members of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. In addition, Shea is a member of the Institute for BioNanotechnology in Medicine and the Chemistry of Life Processes Institute.

Clinical Trial For Ms Tests Same Approach—With Key Difference

The study’s method is the same approach now being tested in multiple sclerosis patients in a phase I/II clinical trial—with one key difference. The trial uses a patient’s own white blood cells—a costly and labor intensive procedure—to deliver the antigen. The purpose of the new study was to see if nanoparticles could be as effective as the white blood cells as delivery vehicles. They were.

The Big Nanoparticle Advantage For Immunotherapy

Nanoparticles have many advantages; they can be readily produced in a laboratory and standardized for manufacturing. They would make the potential therapy cheaper and more accessible to a general population. In addition, these nanoparticles are made of a polymer called Poly(lactide-co-glycolide) (PLG), which consists of lactic acid and glycolic acid, both natural metabolites in the human body. PLG is most commonly used for biodegradable sutures.

The fact that PLG is already FDA approved for other applications should facilitate translating the research to patients, Shea noted. Miller and Shea tested nanoparticles of various sizes and discovered that 500 nanometers was most effective at modulating the immune response.

"We administered these particles to animals who have a disease very similar to relapsing remitting multiple sclerosis and stopped it in its tracks," Miller said. "We prevented any future relapses for up to 100 days, which is the equivalent of several years in the life of an MS patient."
Shea and Miller also are currently testing the nanoparticles to treat Type one diabetes and airway diseases such as asthma.

**Nanoparticles Fool Immune System**

In the study, researchers attached myelin antigens to the nanoparticles and injected them intravenously into the mice. The particles entered the spleen, which filters the blood and helps the body dispose of aging and dying blood cells. There, the particles were engulfed by macrophages, a type of immune cell, which then displayed the antigens on their cell surface. The immune system viewed the nanoparticles as ordinary dying blood cells and nothing to be concerned about. This created immune tolerance to the antigen by directly inhibiting the activity of myelin responsive T cells and by increasing the numbers of regulatory T cells which further calmed the autoimmune response.

"The key here is that this antigen/particle-based approach to induction of tolerance is selective and targeted. Unlike generalized immunosuppression, which is the current therapy used for autoimmune diseases, this new process does not shut down the whole immune system," said Christine Kelley, National Institute of Biomedical Imaging and Bioengineering director of the division of Discovery Science and Technology at the National Institutes of Health, which supported the research. "This collaborative effort between expertise in immunology and bioengineering is a terrific example of the tremendous advances that can be made with scientifically convergent approaches to biomedical problems."

"We are proud to share our expertise in therapeutics development with Dr. Stephen Miller’s stellar team of academic scientists," said Scott Johnson, CEO, president and founder of the Myelin Repair Foundation. "The idea to couple antigens to nanoparticles was conceived in discussions between Dr. Miller’s laboratory, the Myelin Repair Foundation’s drug discovery advisory board and Dr. Michael Pleiss, a member of the Myelin Repair Foundation’s internal research team, and we combined our efforts to focus on patient-oriented, clinically relevant research with broad implications for all autoimmune diseases. Our unique research model is designed to foster and extract the innovation from the academic science that we fund and transition these technologies to commercialization. The overarching goal is to ensure this important therapeutic pathway has its best chance to reach patients, with MS and all autoimmune diseases."

**Skin cells reveal DNA’s genetic mosaic ***

The prevailing wisdom has been that every cell in the body contains identical DNA. However, a new study of stem cells derived from the skin has found that genetic variations are widespread in the body’s tissues, a finding with profound implications for genetic screening, according to Yale School of Medicine researchers.

"We found that humans are made up of a mosaic of cells with different genomes," said lead author Flora Vaccarino, M.D., the Harris Professor of Child Psychiatry at the Yale Child Study Center. "We saw that 30 percent of skin cells harbor copy number variations (CNV), which are segments of DNA that are deleted or duplicated. Previously it was assumed that these variations only occurred in cases of disease, such as cancer. The mosaic that we've seen in the skin could also be found in the blood, in the brain, and in other parts of the human body."

The longstanding belief has been that our cells have the same DNA sequence and this blueprint governs the body's functions. The Yale team's research challenges this dogma. Some scientists have hypothesized that during development, when DNA is copied from mother to daughter cells, there could be deletions, duplications and changes in the sequence of the DNA, and an entire group of genes could be affected. This premise has been incredibly difficult to test, but Vaccarino and colleagues have done so in this new study.

The team used whole genome sequencing to study induced pluripotent stem cells lines (iPS), which are stem cells developed from a mature-differentiated cell. The team grew cells taken from the inner upper arms of two families. The team spent two years characterizing these iPS cell lines and comparing them to the original skin cells.

While observing that the genome of iPS cells closely resembles the genome of skin cells from which they originated, the team could identify several deletions or duplications involving thousands of base pairs of DNA. The team then performed additional experiments to understand the origin of those differences, and showed that at least half of them pre-existed in small fractions of skin cells. These differences were
revealed in iPS cells because each iPS line is derived from one, or very few, skin cells. Vaccarino said these iPS lines could act as a magnifying glass to see the mosaic of genomic differences in the body's cells.

"In the skin, this mosaicism is extensive and at least 30 percent of skin cells harbor different deletion or duplication of DNA, each found in a small percentage of cells," said Vaccarino. "The observation of somatic mosaicism has far-reaching consequences for genetic analyses, which currently use only blood samples. When we look at the blood DNA, it's not exactly reflecting the DNA of other tissues such as the brain. There could be mutations that we're missing."

"These findings are shaping our future studies, and we're doing more studies of the developing brains of animals and humans to see if this variation exists there as well," Vaccarino added.

**Washington Post Examines Polio Eradication Efforts In Pakistan**

The Washington Post reports on polio eradication efforts in Pakistan, writing, "[O]verall trends in Pakistan, where nearly 30 million children have been vaccinated in recent years, are encouraging." The newspaper writes, "Last year's cases numbered 198 nationwide," adding, "This year's tally is 54."

However, "the intractability of other social ills, including insurgency, poverty, illiteracy and inadequate sanitation, have conspired to ensure that the country remains years away from meeting its goal of polio eradication by the dawn of 2013," the newspaper notes. The Washington Post discusses a number of challenges to vaccination efforts, such as a Taliban ban on vaccinations and fear among some parents that "the drops contain religiously proscribed ('non-halal') ingredients or are part of a Western plot to spread infertility and limit Muslim population growth." The newspaper adds, "One key to reducing outbreaks, U.N. health workers say, is to educate parents" (Leiby, 11/16).

**HIIT and FIMM researchers excel in predicting cancer drug sensitivity in an international crowdsourcing challenge**

14.11.2012

Researchers from Helsinki Institute for Information Technology HIIT and Institute for Molecular Medicine Finland FIMM have developed a triumphant solution for predicting responses of breast cancer cells to a set of cancer drugs. The prediction is based on the genomic profiles of the cancer cells. Harnessing genomic profiles of cells in choosing the best treatment is considered the holy grail of personalised medicine.

The team participated in the seventh annual DREAM competition organised by the U.S. National Cancer Institute (NCI) and The Dialogue for Reverse Engineering Assessments and Methods (DREAM). Their challenges crowd-source highly demanding scientific problems to top research teams around the world. The best solution will be published in a top journal.

The team led by Professor Samuel Kaski, Director of HIIT, a joint research centre of Aalto University and University of Helsinki, will present its winning solution at the DREAM 2012 conference on November 13 in San Francisco. The team's solution outperformed 47 other teams in the prediction challenge.

**Computational methods integrate multiple views of the genomic profile of cancer cells**

It is well known that drug therapies may effectively kill cancer cells in one patient, but not in another patient suffering from the same type of cancer. However, the molecular determinants underlying the differences in drug response are not sufficiently understood.

A goal of computational personalised medicine is to develop models which predict drug sensitivity of cells from their genomic profiles, explains Kaski.

The organisers of the NCI-DREAM challenge provided data of breast cancer cells for the training of computational sensitivity prediction models. They evaluated the participants’ models on test measurements of drugs that were unknown to the participants.

As in most current biomedical experiments, several types of measurements had been collected on the cancer cells: activity of genes, epigenetics, and genetic profiles. The key problem was to optimally combine the complementary “views” that the different measurements yield.

We had been developing new machine learning methods for these ‘multi-view’ problems, which occur in many fields, and they gave us a flying start, tells Kaski.

HIIT and FIMM have also collaborated on personalised medicine well before the competition.

The challenge was a great additional opportunity for us to put our heads together. People with different backgrounds presented different views on the problem and brought in their own expertise and experience to improve the integrated solution, says HIIT researcher Dr. Elisabeth Georgii.
Although the result is still far from clinical applicability, computational personalised medicine has taken an encouraging, prize-winning step forward.

**Multiple sclerosis 'immune exchange' between brain and blood is uncovered**

UCSF finding of movement with disease-causing B cells gives hope for new treatments and diagnostics

DNA sequences obtained from a handful of patients with multiple sclerosis at the University of California, San Francisco (UCSF) Medical Center have revealed the existence of an "immune exchange" that allows the disease-causing cells to move in and out of the brain.

The cells in question, obtained from spinal fluid and blood samples, are called B cells, which normally help to clear foreign infections from the body but sometimes react strongly with the body itself. One of the current theories of multiple sclerosis, which strikes hundreds of thousands of Americans and millions more worldwide, holds that the disease manifests when self-reactive B cells in the brain become activated and cause inflammation there.

The apparent exchange of the cells between the brain and the blood may be a key to unlocking better treatments and diagnostics, because the activated B cells causing problems in the brain may be accessible when they move from the brain to the periphery.

"The hope is that if we can identify culprit B cells, using precise tools, we will be able to better diagnose multiple sclerosis and monitor disease activity. In addition, in ways that may have to be tailored for each patient, this may also allow us to develop therapies that directly target disease-causing B cells," said UCSF neurologist Hans Christian von Büdingen, MD, who led the research.

Described this week in the *Journal of Clinical Investigation*, the work is the latest from the UCSF Multiple Sclerosis Center, part of the UCSF Department of Neurology and one of the leading programs in multiple sclerosis research and patient care worldwide.

Since 2008, a UCSF team led by the chair of the Department of Neurology, Stephen Hauser, MD, has completed two clinical trials that showed, in essence, that blocking B cells may stop the attacks, or flare-ups, that occur in people with multiple sclerosis. These trials used Rituximab and Ocrelizumab, both of which target a molecule called CD20 found on the surface of B cells.

The new work suggests that targeting B cells could be extended into a precision strategy that would specifically tailor treatments to the exact identity of the B cells at work in any one patient.

**Background on B cells and Multiple Sclerosis**

Multiple sclerosis is a common, chronic disease affecting some 350,000 Americans whose immune systems periodically attack the myelin sheaths that insulates nerve fibers in the brains and spinal cord. Damage to the sheaths can short-circuit signals traveling along the nerve fibers, disrupting the normal flow of communication from the brain and causing a range of symptoms.

The disease is about three times more prevalent among women than men, and for reasons scientists do not understand, the number of women who have the disease has been increasing in proportion to men. Decades ago, there were about as many men as women with multiple sclerosis.

That disparity is not the only mystery surrounding multiple sclerosis. The severity of the disease can vary wildly, from people who have mild disease, rarely having symptoms, to people who suffer significant deficits for long periods of time, sometimes progressively, with weakness, sensory disturbance, fatigue, visual impairments and loss of coordination. In addition, scientists do not understand what triggers MS attacks, though researchers at UCSF and elsewhere are actively investigating a number of possible genetic and environmental triggers, including low vitamin D levels.

There also is a need to find better ways to diagnose, monitor and track the disease – a need that may be helped by the new discovery.

"We don't have any specific diagnostic tool at this point – no biomarker that we can look for to say, 'this is multiple sclerosis','" von Büdingen said.

The article, "B cell exchange across the blood-brain barrier in multiple sclerosis" by H.-Christian von Büdingen, Tracy C. Kuo, Marina Sirota, Christopher J. van Belle, Leonard Apeltsin, Jacob Glanville, Bruce A. Cree, Pierre-Antoine Gourraud, Amy Schwartzburg, Gabriella Huerta, Dilduz Telman, Purnima D. Sundar, Tyler Casey, David R. Cox and Stephen L. Hauser was published online by the *Journal of Clinical Investigation* on Nov. 19, 2012. See: http://dx.doi.org/10.1172/JCI63842

**Plant Derivative, Tanshinones, Protects Against Sepsis, Study Suggests**

ScienceDaily (Nov. 15, 2012) — Researchers at The Feinstein Institute for Medical Research have discovered that tanshinones, which come from the plant Danshen and are highly valued in Chinese
traditional medicine, protect against the life-threatening condition sepsis. The findings are published in the December issue of *Biochemical Pharmacology*.

Inflammation is necessary for maintaining good health—without inflammation, wounds and infections would never heal. However, persistent and constant inflammation can damage tissue and organs, and lead to diseases such as sepsis. Sepsis affects approximately 750,000 Americans each year, 28 to 50 percent of whom die from the condition, and costs the nation’s healthcare system nearly $17 billion annually. It is a potentially life-threatening complication of an infection or injury, and occurs when chemicals released into the bloodstream to fight the infection trigger inflammation throughout the body. The result is that organs become damaged, including liver, heart, lungs, kidney and brain. If excessive damage occurs, it may be irreversible. For years, Feinstein Institute researchers have been trying to identify ways to halt persistent and constant inflammation.

Tanshinones have been used for treatment of cardiovascular and cerebrovascular diseases. Based on research on mice conducted by Haichao Wang, PhD, and his colleagues, including Kevin J. Tracey, MD, and Andrew E. Sama, MD, at the Feinstein Institute, tanshinone IIA sodium sulfonate (TSN-SS) effectively inhibited the release of HMGB1 outside of cells. HMGB1 is a deoxyribonucleic acid (DNA) protein that mediates inflammation and, if over expressed, causes sepsis. Furthermore, Dr. Wang and his colleagues previously discovered that inhibition of HMGB1 by TSN-SS protected against sepsis-induced animal mortality and cardiovascular dysfunction in animals.

"Dr. Wang’s research on TSN-SS has uncovered details that offer a new mechanism for intracellular drug delivery," said Sarah Dunsmore, Ph.D., of the National Institutes of Health’s National Institute of General Medical Sciences, which partially supported the work. "These findings have broad significance and implications for treating a variety of conditions, including cancer, sepsis and Alzheimer's disease."

"This novel therapy opens up more applications for the use of Chinese traditional medicine in western medicine, and it is my hope that it will be tested for efficacy in sepsis clinical trials in the near term." said Dr. Wang.

**Journal Reference:**

### Influenza Curbs Part of Immune System and Abets Bacterial Infections

ScienceDaily (Nov. 15, 2012) — When infected with influenza, the body becomes an easy target for bacteria. The flu virus alters the host’s immune system and compromises its capacity to effectively fight off bacterial infections. Now, a team of immunologists at the Helmholtz Centre for Infection Research (HZI) and cooperation partners has discovered that an immune system molecule called TLR7 is partly to blame. The **molecule recognizes the viral genome—and then signals scavenger cells of the immune system to ingest fewer bacteria.** The researchers published their findings in the *Journal of Innate Immunity.*

The flu is not just a seasonal illness during the winter months. In the past, there have been several flu pandemics that have claimed the lives of millions. By now, we know that during the course of the disease, many people not only get sick from the flu itself but also from bacterial pathogens like the much-feared pneumococci, the bacteria causing pneumonia. In many cases, such "superinfections" can cause the disease to take a turn for the
worse. In fact, during the Spanish Flu of 1918 to 1920, they were responsible for the majority of deaths. Why an infection with the flu virus increases the risk for superinfections is still poorly understood. Now, a group of scientists from HZI, the University Hospital of the Otto von Guericke University Magdeburg, the Essen University Hospital, the Karolinska Institute in Stockholm, Sweden, as well as further research institutions have discovered one more detail on how the virus manipulates the immune system.

They focused on **TLR7, a molecule that is found in different cells of the body. TLR7 is capable of recognizing viral genetic material.** As it turns out, TLR7 has an unwanted side effect, too: **During a flu infection, it appears to undermine the body's innate ability to fight off bacteria, thereby increasing the chance of a superinfection.** The researchers made their discovery when they examined how superinfected mice were dealing with the bacterium *Streptococcus pneumoniae*, the pneumonia pathogen. The scientists colored the bacteria and measured how many of them were taken up by scavenger cells of the immune system called macrophages. The **macrophages of TLR7-deficient mice had a bigger appetite and eliminated larger numbers of bacteria when infected with the flu than those of mice with the intact viral sensor.** "Without TLR7, it takes longer before influenza-infected mice reach the critical point where they are no longer able to cope with the bacterial infection," explains Prof. Dunja Bruder, head of HZI's "Immune Regulation Group" and professor of infection immunology at the University Hospital Magdeburg.

The scientists also have an idea about how TLR7 may be curtailing the scavenger cells' appetite: Whenever the immune system recognizes a virus, it gets other immune cells to produce a signaling substance called IFN gamma. It is already known that this substance inhibits macrophages in the lungs, causing them to eliminate fewer bacteria. As part of their study, the researchers discovered another indication of this special relationship: In TLR7-deficient animals they found smaller quantities of the IFN gamma messenger substance. The consequence might be that macrophages have a bigger appetite and that therefore bacterial entry into the bloodstream is delayed.

"Our results confirm that in the long run the flu virus suppresses the body's ability to defend itself against bacteria. Presumably, this is an unwanted side effect of the viral infection," speculates Dr. Stegemann-Koniszewski, the study's first author.

"Unfortunately, it is rather difficult to intervene therapeutically. At first glance, it seems obvious to inhibit TLR7 during influenza so that the macrophages are actually able to get rid of the bacteria. However, this could have unforeseen repercussions as TLR7 and IFN gamma are both part of a tightly regulated immunological network," explains Prof. Matthias Gunzer, former research group leader at the HZI and currently a professor at Essen University Hospital.

Even if a lack of TLR7 cannot by itself ward off a bacterial superinfection, the researchers' findings could still lead to highly promising potential clinical applications. "Missing TLR7 delays the spread of bacteria via the bloodstream," says Bruder. "Even if we are only talking about a relatively brief window of time, this might be our critical opportunity for keeping a seriously ill patient alive. The more time doctors have to choose the right antibiotic for their patient, the better the chances of a successful treatment."

**Journal Reference:**
Sabine Stegemann-Koniszewski, Marcus Gereke, Sofia Orrskog, Stefan Lienenklaus, Bastian Pasche, Sophie R. Bader, Achim D. Gruber, Shizuo Akira, Siegfried Weiss, Birgitta Henriques-Normark, Dunja Bruder, Matthias Gunzer. **TLR7 Contributes to the Rapid Progression but Not to the Overall Fatal Outcome of Secondary Pneumococcal Disease following Influenza A Virus Infection.** *Journal of Innate Immunity*, 2012; DOI: 10.1159/000345112

**Anthrax Detection**
Mike Mitka, MSJ  

The federal government's ability to detect *Bacillus anthracis* remains flawed, the Government Accountability Office (GAO) reported September 11. The report comes 11 years after spores of *B anthracis*, the bacterium that causes anthrax, were mailed to members of Congress and the media in a still-unsolved bioterror attack. A 2005 GAO report recommended that federal agencies validate environmental sampling methods for detecting *B anthracis* and conduct studies to develop probability-based sampling approaches for indoor environments. Such activities were to be completed by fiscal year 2013, but delays are now expected.
New fixed-dose combination pills measure up to Atripla

Gus Cairns
Published: 20 November 2012

Several studies, or updates of studies, comparing newer against older drug regimens were presented at the Eleventh International Congress on Drug Therapy in HIV Infection last week.

Amongst them were the 48-week results from the STAR study, an open-label study comparing the new-generation NNRTI drug (non-nucleoside reverse transcriptase inhibitor), rilpivirine, with the first-generation efavirenz, not as themselves, but in their one-pill once-a-day guises as Atripla (tenofovir/FTC plus efavirenz) and Eviplera (tenofovir/FTC plus rilpivirine: called Complera in the US).

This is the first time these two one-pill fixed-dose combinations have been directly compared with each other.

Also presented were the 96-week results of two placebo-controlled studies comparing Gilead’s new ‘Quad’ pill Stribild against either Atripla or tenofovir/FTC (Truvada) and ritonavir-boosted atazanavir (ATV/r: Reyataz/Norvir). Stribild contains tenofovir and FTC and the integrase inhibitor elvitegravir plus cobicistat, a drug developed by manufacturers Gilead as an alternative to ritonavir and which, like ritonavir, boosts the blood levels of elvitegravir to effective levels rather than acting against HIV itself.

Eviplera superior to Atripla for high viral loads, but more resistance cases

The STAR study was conducted as an open-label study because the licensing studies of rilpivirine, ECHO and THRIVE, did not compare the fixed-dose combinations but efavirenz and rilpivirine separately, in combination with Truvada (tenofovir/FTC) or, in the case of THRIVE, sometimes two other nucleoside (NRTI) drugs. This meant that, because the studies also included placebos of whatever drug the patient was not actually taking, people were taking at least three pills a day and sometimes more.

The STAR study compared viral suppression, CD4 count rises, resistance, adverse events and blood lipids in 392 treatment-naïve people taking Eviplera against 392 taking Atripla, without placebos. The mean CD4 count of those starting was 390 cells/mm³ and the mean viral load 63,000 copies/ml (4.8 logs). After 48 weeks, 86% of those on Eviplera and 81% on Atripla had a viral load below 50 copies/ml. This percentage difference was not statistically significant (95% confidence interval -1.2 to +9.2).

But it was significantly different in people who started treatment with a viral load over 100,000 copies/ml: here 88% of people on Eviplera and 81% on Atripla had an undetectable viral load; this 7% difference had a 95% confidence interval of +0.9 to +13.2, meaning that Eviplera was not just ‘non-inferior’ to Atripla, but superior in terms of the primary outcome of viral suppression.

Nonetheless, although viral suppression failure rates on rilpivirine were lower, there was concern that there would be more drug resistance seen in those whose regimens did fail. This had been seen in ECHO and THRIVE and was a reason rilpivirine was not immediately adopted as an NNRTI of choice for first-line therapy.

Resistance rates were not as high in STAR. The percentage of people developing drug resistance on Eviplera was 4%, as opposed to 7% in the other two studies (pooled average), and in people starting therapy with a viral load over 100,000 copies/ml it was 5%, as opposed to 8%. In contrast, resistance rates to Atripla were just 1% in STAR and 2% in ECHO and THRIVE.

However, in the small number of people with baseline viral loads over 500,000 copies/ml, 18% on Eviplera in STAR developed resistance compared to 4% on Atripla and this may indicate the need for continued caution in using rilpivirine in people with very high viral loads.

In contrast, there were more adverse events in people taking Atripla. These were mainly due to the well-known psychological and neurological side-effects of efavirenz. Fifty-seven per cent of study participants on Atripla had a psycho-neurological adverse event compared with 30% on Eviplera; especially marked was the difference in dizziness (26% on Atripla versus 8% on Eviplera) and there were also differences in dreams, sleep patterns and feeling sleepy during the day.

Other differences between the two drugs were not so marked; for instance, although the efavirenz in Atripla raised total cholesterol by 22% whereas it stayed largely the same in people on Eviplera, efavirenz also raised ‘good’ HDL-cholesterol, meaning that the total/HDL cholesterol ratio, which is probably the best guide to cardiovascular risk, remained unchanged.

Stribild non-inferior to efavirenz or atazanavir but unexplained failure rate in women

The 96-week results from the 102 and 103 double-blind placebo-controlled trials of Stribild differed little from the 48-week results already presented and analysed, most recently last September.

In study 102, Stribild is being compared with Atripla and in 103, with Truvada/atazanavir/ritonavir. The studies are being continued till week 192.
At 96 weeks, 84% of participants in trial 102 and 83% in trial 103 on Stribild had viral loads under 50 copies/ml compared with 82% taking the other drugs in both trials. Failure due to non-suppression of viral load, as opposed to other reasons like drop-outs and side-effects, was 6% for Stribild in either study, 8% for Atripla and 8% for ATV/r.

In the 103 trial, an analysis was presented of differential success rates for different populations. For instance, younger people (under 40) did better on Stribild with 83% having a viral load under 50 copies/ml at week 96, against 77% on ATV/r. In comparison 88% of older people had a viral load under 50 copies/ml on ATV/r compared with 84% on Stribild.

One safety concern with Stribild is that a number of cases of decline in kidney function have been seen: these seem to be related to cobicistat rather than the other drugs. At 96 weeks, there was a difference in trial 103: serum creatinine (a waste product that kidneys should eliminate and which is a measure of kidney efficiency) had risen by 0.13 mg/dl in Stribild patients and only 0.01 mg/dl in patients on ATV/r.

One result stood out, however, that is worrying and so far has not been explained. There were very few women in these studies; just 12% in 102 and 10% in 103 were women, and the failure to recruit women was criticised in this conference, most notably by community co-chair Brian West, chair of EATG, in his closing remarks.

This means that there were just 154 results from women out of 1400 participants in total. But lower virological suppression rates were seen in women, notably on Stribild and notably in the 70 women in 103, where 74% taking ATV/r achieved a viral load under 50 copies/ml, but only 59% (17 out of 29) taking Stribild. Whether these 12 failures, which are much higher proportionately but lower numerically than in men (47 men experienced treatment failure on Stribild) is just a statistical fluke or linked to a gender characteristic will hopefully be answered when further studies currently being conducted in women and children publish their results.

References

Texas Biomed files patent for a novel HIV vaccine strategy November 19, 2012 in HIV & AIDS
The Texas Biomedical Research Institute in San Antonio has applied for a patent for a genetically-engineered vaccine strategy to prevent HIV infection that targets the outer layers of body structures that are the first sites of contact with the virus. Ads by Google Vaccine Research Reagents—2000+ Protein, Antibody, ELISA Kits, Recombinant Viral Proteins, cDNA—www.SinoBiological.com/Antibody Stem Cell Rejuvenation—Stem cell therapy center US-based autologous treatment—www.the-stem-cell-center.com Designed to be a single dose and last a lifetime, the vaccine will lead to the continual production of disease-fighting cells without being eliminated by the immune system. Another feature of the vaccine system is that it could be adapted for use against other infections. More than 90 percent of new HIV infections worldwide are transmitted by sexual intercourse through outer layers of cells called epithelial cells which line the surfaces of structures throughout the body. The new vaccine is directed to what are known as the mucosal layers of the epithelium in the genital and rectal areas where the virus enters the body. "The development of an effective AIDS vaccine that restricts viral replication at the mucosal level of entry may be our best hope for controlling the HIV pandemic," said Marie-Claire Gauduin, Ph.D., of Texas Biomed’s Department of Virology and Immunology, who is a co-inventor on the patent with Philippe Blancou, Ph.D., a visiting scientist from the University of Nice-Sophia Antipolis, France. "Only life-long stimulation of the immune system by the vaccine will be sufficient to achieve long-term protection," she added. One of the main reasons for the failure of HIV vaccines thus far is their inability to deliver antibody-producing cells for prolonged periods of time, thus only achieving weak and transient protection at best. The primary target for viral transmission through different mucosal sites varies depending on the tissue. However, soon after crossing the mucosal layer, HIV rapidly spreads to lymph nodes and other organs where it replicates. The vaccine will have a molecule and stem cell gene...
tagged to target epithelial cells, that combined, will promote the production of antibody-producing cells. Thus, the epithelial layer will continuously release new antibody-producing cells and not be eliminated by the body's immune response.

Military Reverses Course on HIV+ People Serving Overseas
Navy Releases Major Updates to Service Member HIV Policy
By Katie Miller
This past year, the United States hosted the 19th International AIDS Conference for the first time since 1990. Although the United States has established itself as a global leader in HIV/AIDS research and funding, it wasn't until 2010 that the government lifted the entry ban on HIV positive people wishing to travel to America, thereby making the International AIDS Conference possible in this country. Before then, the United States stood out as one of only a handful of countries worldwide that barred people living with HIV from visiting or immigrating to the country.

However, the U.S. military continues its own form of a travel ban. Military policy prohibits HIV-positive service members from being stationed outside the United States. But on Aug. 13 the Pentagon quietly released a revision to the Department of the Navy policy, which now allows HIV-positive Sailors to be stationed at U.S. military installations outside of the country and on select large ship platforms. The policy change, listed under Secretary of the Navy Instruction (SECNAVINST) 5300.30E, is intended to “reflect current knowledge” of HIV and marks the biggest change in military HIV policy since the late 1980s when mass testing for HIV went into effect. Though the update removes logistical barriers to service, it does nothing to dissolve the space for discrimination which falls under commanders' discretion. As long as the policy allows good Soldiers, Sailors, Airmen, and Marines to be subjected to the prejudices of their superiors, our mission of equality in the military will be unaccomplished.

An Overview of U.S. Military HIV Policies
Although each branch of service maintains its own policies relating to HIV-positive people, the services have several major commonalities. First, all service members are tested for HIV every two years at a minimum, when given overseas assignments and when reservists transition to active duty.

The second commonality concerns enlistment; people with HIV are not eligible for general enlistment or enrollment in officer accession programs. The medical evaluation mandates all potential enlistees be physically and psychologically equipped to survive battlefield conditions. Unsurprisingly, those dependent on prescription medication are unqualified for service, as the military cannot guarantee access to medications in all situations. HIV, which causes immune deficiency, poses an additional risk for potential enlistees because of mandatory live-virus vaccinations administered at basic training, which could be deadly for persons living with the virus. This section of the policy is uncontested.

The third addresses retention of personnel who become HIV positive while serving in the armed forces. When service members are notified of their status, they undergo a separate medical evaluation to determine if they are fit to continue serving. If they wish to remain in the service and the medical evaluations yield positive reviews, they are reassigned to posts near military medical facilities that retain an infectious disease doctor. For those serving overseas, this means relocating to a post within the continental United States. The entire duration of an HIV-positive member’s careers will be spent stateside for the purpose of visiting an infectious disease doctor every three to six months, so OCONUS assignments and deployments are prohibited.

Interestingly, cadets and midshipmen enrolled in officer accession programs are not eligible to continue serving, regardless of physical condition. However, if a cadet or officer candidate is prior service, a return to enlisted status is allowed if his or her contract has not yet ended.

Finally, the military issues “safe sex” orders to personnel with HIV, informing them that they will be criminally prosecuted if they fail to disclose their status to sexual partners or engage in unprotected sex. Similar laws are in effect in a majority of U.S. states, though ranging in extremity.

The Impact on Service Members with HIV
OutServe Magazine interviewed three active-duty, HIV-positive Soldiers and Sailors and an LGBT health professional about military HIV policies and their impact on service members. Names have been changed to protect the identities of the service members.

When asked about the quality of health care they received, the three service members were unanimously positive. Roger, an NCO and moderator of what was previously known as the OutServe HIV Working Group, said, “My care is better in the military than it would be in the civilian world. I don’t have to worry about the cost of medication. It’s mandatory for us to go see the doctor regularly.”
Alex, a junior officer in the Navy, concurred. He expressed considerable praise of the hospital personnel, who offered to reach out to his friends and family to help them learn more about HIV. “I had about seven friends who came in, sat down with someone from the infectious disease clinic, and talked with the staff. The hospital said to me, ‘Alex, if they’re important to you, it’s important that we educate them.’ It was phenomenal.”

But outside of the medical facilities, service members with HIV face a different challenge that military has yet to address: the possible prejudices of their units. Because HIV-positive personnel take TDY every three to six months for medical testing, it’s imperative that command be aware of a service member’s ongoing needs.

Alex found himself rather fortunate in this regard. “It would be bad if someone gave me a negative fitness report. I’ve heard horror stories like that, but that hasn’t been my experience. I’ve been met with nothing but understanding from my unit. They’re like, ‘Everyone has medical issues. Take care of yourself. That’s what’s important.’”

Roger also felt lucky to be part of an accepting unit, but realized his experience is not universal. “It’s not going to be like that for everybody. It’s not going to be this good across the board.”

Matthew Rose, formerly of the National Coalition for LGBT Health and friend of OutServe-SLDN, describes military HIV policy as similar to “Don’t Ask, Don’t Tell.” He explained: “If you get the right commanding officer, your life can be good. Some people were out to their units and experienced no problems. But, if you get a commanding officer who doesn’t agree with your sexuality or has preconceived notions about HIV, there’s not much you can do about it.”

Since the disease still carries a significant level of stigma, the autonomy of the commander is the single biggest flaw in military HIV policy, as discrimination is sure to be as rampant in the military community as it is the civilian world. Lack of guidance means room for abuse.

Jesse found himself at the crux of this problem, in the middle of the space left open for discrimination. Since he was enlisted before attending a service academy and has yet to experience any symptoms of HIV, the policy would permit him to leave the academy at the end of the semester and continue serving in the enlisted ranks. However, his company officer immediately took action to separate him from not only the academy but the military altogether because he did not believe people with HIV should be allowed to continue their service. Jesse filed a complaint with the inspector general, which only served to expedite the commander’s intent to separate Jesse.

As policy dictated, Jesse’s enlistment contract was eventually reinstated, and he continues to serve on active duty. But the process demonstrated how current policy left him vulnerable to his command leadership.

The current lack of non-discrimination policies for HIV-positive personnel makes it impossible for the military to abide by industry standard human resources principles that guide many organizations’ personnel policies. One of those standards, procedural justice rules, states that policies must be, among other things, consistent. It must apply equally across all people and time. The current policy does not apply across all people since commanders can make independent decisions regarding the assignments and missions for which HIV-positive service members are eligible. Another principle, interpersonal justice rules, maintains that all employees must be treated with respect. Again, with the lack of a non-discrimination policy in place, commanders have such a high level of individual discretion that can be, at times, disrespectful to those service members.

**Policy Update: Navy Begins the March toward Equality**

One of the issues most important to these servicemen was the ban on overseas assignments. At first glance, the regulation appears to be in the best interest of the service member’s health: because they must regularly visit one of the military’s hospitals with an infectious disease clinic, stateside assignments are closest in proximity and therefore ideal.

Rose argues against this logic. Referring to the U.S. Military HIV Research Program, “The military delivers HIV care in the most impoverished places on the planet, like Sub-Saharan Africa. Yet for some reason, they don’t believe they can deliver care for service members outside the United States. What’s more, in any major industrialized city you can find a [infectious disease] doctor or at least a place that can run labs and interpret results.”

Feasibility aside, the negative impacts of the overseas assignment ban on service members’ careers has become well known in recent years. Roger is quick to note the assignments available often offer little potential for moving up the ranks. When Alex’s commander was informed of his status, she took special care to ensure he would be placed in a position that would not prevent him from being promoted. She ordered, “Do not stick him in a billet that will end his career.”
The updated Navy HIV policy also points to this limitation as having “made this subset of personnel less competitive in achieving career milestones or warrior qualifications.” With HIV resembling more of a “chronic condition than anything else,” says Alex, the only performance barrier for service members with HIV is policy, not physical capability. The Navy and the interview participants agree: current military HIV policies have career-ending effects.

However, the other services have yet to similarly update their policies. Still, recognizing the difference in the nature of deployment for the other branches, the service members we interviewed understood the challenges. Roger stated bluntly, “I don’t believe we should be discussing combat zones. Whether you’re sitting behind a desk in Afghanistan or out doing patrols, everyone has the same risk of getting hurt. Medics don’t have time to consider if a person has HIV or not.”

But he does believe personnel could be managed better. “Take Kuwait, for example. It’s not a combat zone. But when the wars in Afghanistan and Iraq were full on, people were getting sent there, and they could have been used in better places, like in deployable units. All I would need is enough medication for the length of the tour, and I could have taken their place.”

Jesse expressed a similar sentiment. “In my MOS, I’d be doing the same thing in Kuwait that I would be doing in the United States. It wouldn’t change. I hope to stay in the military for a long time, and if my subordinates look at me and see that I don’t have any time overseas, they’re not going to respect me.”

OutServe-SLDN Executive Director, Allyson Robinson, applauds the Navy’s first step toward ending HIV-discrimination in the military and their efforts to remove barriers to career advancement for Sailor and Marines. But Robinson, an Army veteran and West Point graduate, also points out that the policy does nothing to ensure commanders do the right thing:

“The new policy is a modest improvement at best. The latitude it gives to individual commanders to deny these newly opened assignments to HIV-positive Sailors and Marines will likely prove problematic. Misinformation, stigma, and stereotypes should never be allowed to dictate military assignments. Until that kind of discrimination is prevented, policy changes like this may prove not to be worth any more than the paper they’re printed on.”

As President Barack Obama stated when the HIV travel ban was ended in 2009, “If we want to be the global leader in combating HIV/AIDS, we need to act like it.” And if America is going to lead the world in ending the pandemic, properly addressing it in its own armed forces would be a good starting point. Although many of the military’s health and personnel policies are satisfactory, further updates are obviously needed to reflect current knowledge of the virus and to remove the stigma which has pervaded policy formation in the past. With the release of the new policy, the Navy has raised the bar for equality in the military. But consistent with all tasks in the military, the only commendable performance is one which not only meets, but exceeds the standard.

**Sudan Launches Yellow Fever Vaccination Campaign To Immunize 2.4M**

"Sudan has launched a massive vaccination campaign to immunize 2.4 million people against an outbreak of yellow fever in the restive region of Darfur, the U.N. said Monday," according to the Associated Press. "The U.N. Office for the Coordination of Humanitarian Affairs said Khartoum’s health ministry received an initial shipment of 800,000 doses of vaccine on Friday to battle the outbreak, which began in September after a heavy rainy season created additional breeding sites for disease-carrying mosquitoes," the news service writes, adding, "As of Saturday, Sudan had reported 116 deaths out of 459 suspected cases" (Osman, 11/19).

November 20, 2012

**Sweat glands play major role in healing human wounds, U-M research shows**

As poor wound healing from diabetic ulcers and other ailments takes heavy toll on healthcare costs, U-M findings pave way for new efficient therapies

ANN ARBOR, Mich. — Turns out the same glands that make you sweat are responsible for another job vital to your health: they help heal wounds.

Human skin is rich with millions of eccrine sweat glands that help your body cool down after a trip to the gym or on a warm day. These same glands, new University of Michigan Health System research shows, also happen to play a key role in providing cells for recovering skin wounds – such as scrapes, burns and ulcers.

The findings were released online ahead of print in the American Journal of Pathology.
“Skin ulcers – including those caused by diabetes or bed sores – and other non-healing wounds remain a tremendous burden on health services and communities around the world,” says lead author Laure Rittié, Ph.D., research assistant professor of dermatology at the University of Michigan Medical School.

“Treating chronic wounds costs tens of billions of dollars annually in the United States alone, and this price tag just keeps rising. Something isn’t working.”

Now, U-M researchers believe they have discovered one of the body’s most powerful secret weapons in healing.

“By identifying a key process of wound closure, we can examine drug therapies with a new target in mind: sweat glands, which are very under-studied,” Rittié says. “We’re hoping this will stimulate research in a promising, new direction.”

Previous understanding of wound closure was that new skin cells originate from hair follicles and from intact skin at the edge of the wound. The U-M findings demonstrate that cells arise from beneath the wound, and suggest that human eccrine sweat glands also store an important reservoir of adult stem cells that can quickly be recruited to aid wound healing.

“It may be surprising that it’s taken until now to discover the sweat glands’ vital role in wound repair,” Rittié says. “But there’s a good reason why these specific glands are under-studied – eccrine sweat glands are unique to humans and absent in the body skin of laboratory animals that are commonly used for wound healing research.

“We have discovered that humans heal their skin in a very unique way, different from other mammals,” Rittié adds. “The regenerative potential of sweat glands has been one of our body’s best-kept secrets. Our findings certainly advance our understanding of the normal healing process and will hopefully pave the way for designing better, targeted therapies.”

Additional Authors: Dana L. Sachs, M.D.; Jeffrey S. Orringer, M.D.; John J. Voorhees, M.D.; and Gary J. Fisher, Ph.D., all of the University of Michigan Department of Dermatology.

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Reference: http://dx.doi.org/10.1016/j.ajpath.2012.09.019

How Does Antibiotic Resistance Spread? Scientists Find Answers in the Nose
ScienceDaily (Nov. 20, 2012) — Antibiotic resistance results from bacteria’s uncanny ability to morph and adapt, outwitting pharmaceuticals that are supposed to kill them. But exactly how the bacteria acquire and spread that resistance inside individuals carrying them is not well-established for most bacterial organisms.

Now, University at Buffalo microbiologists studying bacterial colonization in mice have discovered how the very rapid and efficient spread of antibiotic resistance works in the respiratory pathogen, Streptococcus pneumoniae (also known as the pneumococcus). The UB team found that resistance stems from the transfer of DNA between bacterial strains in biofilms in the nasopharynx, the area just behind the nose.

In a paper published in last month’s mBio, the authors found that genetic exchange of antibiotic resistance occurs about 10 million times more effectively in the nose than in the blood of animals, an efficiency far higher than expected.

"The high efficiency of genetic transformation that we observed between bacteria in the nose has a direct clinical implication, since this is how antibiotic resistance spreads, and it's increasing in the population," explains lead author Anders P. Hakansson, PhD, assistant professor of microbiology and immunology in the UB School of Medicine and Biomedical Sciences. "The bacteria 'borrow' each others' DNA in order to become more fit in the host environment and more elusive to the actions of antibiotics."

Hakansson, who also is affiliated with the Witebsky Center for Microbial Pathogenesis and Immunology and the New York State Center of Excellence in Bioinformatics and Life Sciences, performed the study with co-authors Laura R. Marks, an MD/PhD candidate, and Ryan M. Reddinger, a PhD candidate, both in the Department of Microbiology and Immunology at UB. Hakansson explains that the work has opened up a novel direction into the mysteries of how bacteria organize during colonization and how this organization promotes antibiotic spread and the evolutionary fitness of Streptococcus pneumoniae.

Streptococcus pneumoniae is a major colonizer: It's carried in the nasopharynx by essentially everyone by about one year of age. Only occasionally do people get sick from it, but often enough to make
it a leading cause of morbidity and mortality from respiratory tract and invasive infections in children and the elderly worldwide.

"It's rampant in daycare centers and the cause of many childrens' ear infections," Hakansson says. "In developing countries, where fresh water, nutrition and antibiotics are lacking, it is a major cause of disseminating pneumonia leading to sepsis and death of about a million children worldwide, often in combination with virus infections, such as the flu."

The research exposes what Hakansson describes as the puzzling history of studies into the transformation of genetic material between bacteria.

He explains that natural transformation or genetic exchange of DNA in infected mice was first described in 1928 by Frederick Griffith who was studying Streptococcus pneumoniae, because of its role in the Spanish flu epidemic of 1918-1919. Genetic transformation also helped identify DNA as the hereditary material and thus figured in the milestone research of James D. Watson and Francis Crick in determining the structure of DNA.

"Since then, all experiments with pneumococcal transformation have been done artificially in test tubes or in blood infection models," says Hakansson, "even though it's known epidemiologically that genetic exchange occurs almost exclusively when the organism exists in the nose.

"For some reason, no one had looked at how resistance spread in the environment where it really happens, in the nasopharynx," he continues. "So we decided to do that. When we did, we found that the efficiency with which antibiotics spread in the nasopharynx was way above what we expected."

And last summer, the UB researchers published in Infection & Immunity findings showing that when they colonize the nose, pneumococci form sophisticated, highly structured biofilm communities.

"We found that the bacteria make biofilms in the nose that protect against the action of antibiotics, which have a hard time destroying biofilms," says Hakansson. "In addition, we know that some of the bacteria have to die in order to develop good biofilms. So dead bacteria help create good biofilms and provide DNA that other bacteria can take up and use, which is how bacteria spread antibiotic resistance and become more fit."

The mBio paper shows that the environment in the nasopharynx provides ideal conditions for these phenomena to occur.

Journal Reference:

**Sofosbuvir and daclatasvir dual regimen cures most people with HCV genotypes 1, 2, or 3**

Liz Highleyman
A 12-week, once-daily regimen of the hepatitis C (HCV) polymerase inhibitor sofosbuvir and the NS5A inhibitor daclatasvir, without interferon or ribavirin, produced sustained virological response rates for treatment-naive people in the 90 to 100% range, and appeared effective regardless of HCV subtype, IL28B host gene pattern or use of ribavirin, according to a late-blower presentation this week at The Liver Meeting 2012, the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in Boston.

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Last year's approval of the first direct-acting hepatitis C drugs ushered in a new era of treatment, but many patients and providers are awaiting all-oral therapy without pegylated interferon and its difficult side-effects, and – if possible – without ribavirin, which causes anaemia.

It has become difficult to keep track of the numerous investigational anti-HCV drugs in the pipeline and the many different combination regimens under study, but one that stands out is Gilead Sciences' nucleotide analogue polymerase inhibitor sofosbuvir (formerly GS-7977 and before that PSI-7977) together with Bristol-Myers Squibb's first-in-class HCV NS5A replication complex inhibitor daclatasvir (formerly BMS-790062).

Although its mechanism of action is not fully understood, NS5A appears to play an important role in HCV replication in conjunction with the NS5B polymerase. Based on studies to date, NS5A inhibitors plus polymerase inhibitors may be particularly powerful combinations.

Dr Mark Sulkowski, from Johns Hopkins Medical School, and colleagues tested various all-oral combinations of sofosbuvir plus daclatasvir, with or without ribavirin, in an open-label phase 2a trial.

Because this was one of the earlier ribavirin-free regimens to be evaluated, researchers started with easier-to-treat patient populations and moved on to more challenging groups as they saw promising
results. All study participants to date have been treatment-naive, a group with better prospects for a cure than non-responders to prior interferon-based therapy.

The first stage of the study looked at people with easier-to-treat HCV genotypes 2 or 3, randomising them to receive 400mg sofosbuvir plus 60mg once-daily daclatasvir – some with a seven-day sofosbuvir lead-in and some with the addition of 800mg ribavirin – for 24 weeks.

The second stage enrolled people with harder-to-treat HCV genotype 1, about 75% of whom had the most difficult subtype 1a. The first three of these arms received the same doses of sofosbuvir plus daclatasvir, with or without ribavirin, again for 24 weeks. Then two additional arms received the sofosbuvir plus daclatasvir combination, one group with and one without ribavirin, for 12 weeks to test if shorter therapy is feasible.

The study enrolled about 170 total participants in eight study arms. The median age was approximately 54 years. Gender distribution varied across arms, with men making up 36 to 69%. At least 70% were white in all study arms.

The proportion of participants with the favourable IL28B CC gene variant associated with good interferon response ranged from about 20% to nearly 60%; the figure is typically much lower when studying prior null responders. At baseline, approximately 40% had absent to mild fibrosis (Metavir stage F0–F1), about half had moderate to advanced liver disease (F2–F3) and roughly 15% had cirrhosis (F4).

Looking first at the genotype 2/3 participants, 100% achieved rapid virological response (RVR) at week 4 of treatment. This was a modified intent-to-treat, missing = failure analysis. People who missed one evaluation visit were considered lost to follow-up and not counted when calculating results at that time point; however, if they returned they were allowed to continue in the study and included in later evaluations.

After week 4, a single patient experienced viral break-through, one relapsed after treatment, one was temporarily lost to follow-up, and one was lost permanently. Sustained virological response rates at weeks 4, 12, and 24 post-treatment (SVR4, SVR12, and SVR24, respectively) ranged from 88 to 100%. The addition of ribavirin – which plays a role in preventing relapse after treatment – did not improve response rates.

Turning to the genotype 1 participants, all but one person receiving sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks achieved RVR. That individual went on to suppress HCV with further therapy, so end-of-treatment response rates at week 12 or week 24 were 100% across the board.

Among genotype 1 participants treated for 12 weeks, SVR4 and SVR12 rates were 100% in all three regimen arms. All participants went on to achieve SVR24, except for one person who had measurable HCV RNA at post-treatment week 24. Viral genetic sequencing, however, revealed that the new virus was different from the original one, indicating re-infection rather than relapse.

The genotype 1 participants treated for 24 weeks were still undergoing follow-up. However, amongst the 68 participants who had reached post-treatment week 12, all achieved SVR12.

Sofosbuvir and daclatasvir were generally safe and well tolerated. The most common side-effects overall were fatigue, headache and nausea, with no clear patterns across treatment arms. Moderate-to-severe adverse events occurred somewhat more often in the 24-week lead-in arm and the arm receiving ribavirin for 24 weeks, but numbers were too small to draw definitive conclusions. But there was a clear association between use of ribavirin and anaemia: six and five participants in the two triple-therapy arms developed anaemia (haemoglobin < 9 g/dL), compared with none in the ribavirin-sparing arms.

In summary, the researchers concluded that sofosbuvir plus daclatasvir, with or without ribavirin, achieved SVR in more than 93% of participants with HCV genotype 1, 2 or 3. They added that virological response "did not differ according to IL28B genotype, viral subtype or the administration of ribavirin".

It remains to be seen how well sofosbuvir plus daclatasvir will work for prior null responders to interferon. Various other direct-acting HCV drugs under study looked good in treatment-naive patients but have not performed as well in this more difficult-to-treat group.

As promising as the sofosbuvir plus daclatasvir combination appears to date, its fate is uncertain. Earlier this year Gilead indicated that it would no longer pursue development of this particular regimen. Some have suggested that Gilead prefers to focus on combinations including its own investigational NS5A inhibitor GS-5885, allowing the company to produce coformulated combination pills – its speciality in the HIV arena.

Another study presented at the Liver Meeting showed that sofosbuvir plus GS-5885 plus ribavirin led to 100% SVR4 for genotype 1 treatment-naïve patients and all null responders evaluated to date. Gilead is currently testing a new coformulation of sofosbuvir/GS-5885, with and without ribavirin, in treatment-naïve genotype 1 patients.
Notwithstanding company decisions about which investigational agents to test together, once individual drugs are approved and marketed, clinicians and patients will be able to mix and match them.

Reference
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Unprotected sex reported by the majority of sexually active adolescents infected with HIV since birth
Michael Carter
Published: 21 November 2012
Close to two-thirds of sexually active adolescents infected with HIV at birth have had unprotected sex, US investigators report in the online edition of Clinical Infectious Diseases. Many of those initiating sexual activity had a high viral load and harboured drug-resistant strains of virus, potentially placing “their partners at risk for infection with HIV, including infection with drug-resistant virus”.

“Sexual intercourse, while a normal developmental milestone, presents special challenges for PHIV+ (perinatal HIV-positive) youth,” comment the investigators.

Improvements in HIV treatment and care have lead to significant improvements in the prognosis of children who were infected with HIV at birth. Many are now entering adolescence and young adulthood.

Research involving adolescents and young adults infected with HIV through sex showed that many reported unprotected sex after their diagnosis with HIV.

Investigators from the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS) wanted to establish the prevalence and timing of sexual intercourse and the factors associated with sexual initiation and risky behaviour in adolescents who had been infected with HIV since birth.

A total of 330 individuals aged between ten and 18 years were recruited to the study. They completed computer-assisted questionnaires about their sexual behaviour at baseline. Repeat questionnaires were completed at six monthly follow-up appointments.

The mean age on entry to the study was 13.5 years. Approximately half were female and 71% were black. Just over a third (37%) were living with their biological mother. Substance abuse was reported by 17%. The majority had well-controlled HIV infection: 31% had a viral load above 5000 copies/ml and 75% had a CD4 cell count above 500 cells/mm³.

Overall, 28% reported anal or vaginal sex at baseline or during follow-up. The proportion of those who were sexually experienced increased with age. Sexual intercourse was reported by 53% of 16 year-olds and by 87% of 18 year-olds.

Median age at first sexual intercourse was 13 years for boys and 14 years for girls. Boys also reported oral sex at an earlier age than girls (13 vs 15 years).

A same-sex partner was reported by 13% of males and 21% of females.

Initiating sexual activity during follow-up was associated with non-adherence to antiretroviral therapy (HR = 2.87; 95% CI,1.32-6.25, p = 0.008); older age at baseline (HR = 1.55; 95% CI, 1.20-2.01, p = 0.001) and experience of genital touching at baseline (HR = 2.72; 95% CI, 1.01-7.31, p = 0.05).

Overall, 62% of those reporting sexual intercourse (at baseline or initiation during follow-up) reported unprotected sex. Unprotected sex was reported by two-thirds of those reporting anal sex. Four male participants reported anal sex with a male partner; in three instances, this was unprotected.

Factors associated with reporting unprotected sex were living in a household with an annual household income below $20,000 (p = 0.03) and living with a biological relative other than the biological mother (p = 0.04).

A significant proportion (n = 38; 42%) of sexually active participants had a viral load above 5000 copies/ml. Drug-resistance data were available for 37 of these individuals: 30 (87%) were identified as harbouring virus that was resistant to at least one antiretroviral (ARV) and 22% had resistance to drugs from the main three classes of anti-HIV drugs.

“This resistance is permanent, limiting the treatment options both for the PHIV+ youth and their partners,” comment the authors.

The majority (82%) of participants reported knowing they were HIV positive when they first had sex. A third of these individuals disclosed their HIV status to their first sexual partner. Regardless of disclosure, the majority of individuals (83% disclosed; 84% non-disclosed) reported discussing the use of condoms with their partner.
However, rates of condom use were significantly higher among those who disclosed compared to those who did not disclose their HIV status (67 vs 22%, p = 0.04).

“HIV disclosure as well as condom use and adherence should be emphasized, so that sexual partners were empowered to make safe choices”, write the authors.

They conclude, “interventions that enhance ARV medication adherence, consistent condom use, and HIV disclosure to sexual partners are essential as...youth prepare for independent living and transition to adulthood”.

Reference

MTV Special Profiles Young People with HIV

MTV will present a special on December 1 at 7:00 p.m., Eastern Time, which profiles three young people who are HIV-infected. MTV hopes that the special, “I’m Positive,” will become a regular series. In the 30 years that HIV has existed, the virus that causes AIDS has gone from a death sentence to a chronic condition that can be controlled with early detection and a drug regimen; however, many are worried that some people are not taking the condition seriously enough. According to Drew Pinsky, one of the producers of the show, even if HIV does not develop into full-blown AIDS, there are still questions about the long-term health implications of living with HIV and the drugs that are taken to control it.

The three profiles presented in the program reveal a generational divide. One of the three subjects is a California girl who feels in control of the situation in spite of her infection. MTV hopes that the special, “I’m Positive,” will become a regular series. In the 30 years that HIV has existed, the virus that causes AIDS has gone from a death sentence to a chronic condition that can be controlled with early detection and a drug regimen; however, many are worried that some people are not taking the condition seriously enough. According to Drew Pinsky, one of the producers of the show, even if HIV does not develop into full-blown AIDS, there are still questions about the long-term health implications of living with HIV and the drugs that are taken to control it.

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MTV has successfully used documentary-style programming to effectively reach its young viewers with a message; its programming on teenage pregnancy is a prime example. Pinsky declares that young people can relate to peers who are struggling with the HIV problem. MTV originated its “safe sex” campaigns in 1985, and has been working with the Kaiser Family Foundation since 1997 to encourage youth to get tested for HIV. Two in five people infected with HIV each year in the United States are between the ages of 13 and 29—MTV’s target audience. More than 1.1 million Americans are living with HIV infection, according to the CDC.

Study reveals the proteins expressed by human cytomegalovirus

Ribosome-mapping technique may provide insights into other viral proteomes as well

New findings reveal the surprisingly complex protein-coding capacity of the human cytomegalovirus, or HCMV, and provide the first steps toward understanding how the virus manipulates human cells during infection. The genome of the HCMV was first sequenced over 20 years ago, but researchers have now investigated the proteome—the complete set of expressed proteins—of this common pathogen as well.

HCMV is an incredibly successful virus, and it infects most humans on the planet. Birth defects and disease, however, are only known to occur in newborn infants and adults with compromised immune systems, respectively. But, the pathogen also has one of the largest viral genomes on record, with a massive 240,000 base pairs of DNA. (For comparison, the genome of the poliovirus only contains about 7,500 base pairs.)

Noam Stern-Ginossar from the University of California in San Francisco, along with colleagues from the United States and Germany, used a combination of techniques, including ribosome profiling and mass spectrometry, to study HCMV’s proteome. The method could be used to investigate proteins produced by other viruses as well, they say.

The researchers’ findings appear in the 23 November issue of the journal Science, which is published by AAAS, the nonprofit science society.

"The genome of a virus is just a starting point," explained Jonathan Weissman from the University of California, a co-author of the Science report. "Understanding what proteins are encoded by that genome allows us to start thinking about what the virus does and how we can interfere with it... Each of the proteins we’ve identified has the potential to tell us how this virus is manipulating its host cell."

Stern-Ginossar and the other researchers suspected that existing maps of HCMV’s protein-coding potential, based largely on computational methods, were far from complete. So, they began mapping the positions of ribosomes—the cellular organelles in which proteins are synthesized—during an HCMV
infection of human fibroblast cells. With the resulting map, Stern-Ginossar and her colleagues discovered templates for hundreds of previously unidentified proteins that were encoded in corresponding DNA segments of the viral genome, known as open reading frames.

Surprisingly, the researchers found that many of these open reading frames encode for exceptionally short protein sequences (fewer than 100 amino acids). And some of the newly identified open reading frames were even hiding inside other open reading frames, they say.

"A key finding of our work is that each of these templates can encode more than one protein," said Annette Michalski from the Max Planck Institute of Biochemistry in Martinsried, Germany, another co-author of the Science report. "And these extremely short proteins might be more common than we expect."

The researchers applied mass spectrometry to confirm the presence of many unknown viral proteins that had been predicted by mapping the ribosome positions.

In the future, this coupling of ribosome profiling with mass spectrometry might be used to investigate the proteomes of other complex viruses. Eventually, such information could be used to understand how different viruses hijack their hosts' cells for their own purposes.

**Beneficial Microbes Are 'Selected and Nurtured' in the Human Gut**

ScienceDaily (Nov. 20, 2012) — Animals, including humans, actively select the gut microbes that are the best partners and nurture them with nutritious secretions, suggests a new study led by Oxford University, and published November 20 in the open-access journal PLOS Biology.

The Oxford team created an evolutionary computer model of interactions between gut microbes and the lining (the host epithelial cell layer) of the animal gut. The model shows that beneficial microbes that are slow-growing are rapidly lost, and need to be helped by host secretions, such as specific nutrients, that favour the beneficial microbes over harmful ones.

The work also shows that the cost of such selectivity is low: the host only needs to use a very small amount of secretions to retain beneficial microbes that would otherwise have been lost.

"The cells of our bodies are greatly outnumbered by the microbes that live on us and, in particular, in our gut," said Professor Kevin Foster of Oxford University's Department of Zoology, an author of the new paper. "We know that many gut microbes are highly beneficial to us, protecting us from pathogens and helping us with digestion, but quite how such a beneficial mutual relationship evolved, and how it is maintained, has been something of a mystery."

"This research highlights the importance of growth-promoting substances in our ability to control the microbes that live inside us. It shows that nutrients are more powerful when released by the host epithelial cell layer than when coming from the food in the gut, and suggests that controlling our microbes is easier than was previously thought."

Jonas Schulter, also of Oxford University's Department of Zoology and first author of the paper, said: "The inside of our gut is rather like a war zone, with all kinds of microbes battling it out for survival and fighting over territory. Our study shows that hosts only have to secrete a small quantity of substances that slightly favour beneficial microbes to tip the balance of this conflict: it means that favoured microbial species that would otherwise be lost don't just survive on the epithelial surface but expand, pushing any other strains out."

The team's simulations show that cells affected by host epithelial selection are least likely to be lost, and instead persist longest, causing 'selectivity amplification', whereby relatively tiny changes instituted
by the host (in this case a very small amount of secretions of certain compounds) can be amplified to produce a large-scale effect.

The study may have wider implications than the human gut: selectivity amplification may occur in a range of other interactions between hosts and microbes, including the microbes that grow on the surface of corals and the roots of plants.

**Journal Reference:**

**Abacavir: new studies challenge the evidence of reduced potency when viral load is high**
Gus Cairns
Published: 26 November 2012
An analysis of two studies of the new HIV integrase inhibitor dolutegravir presented at the *Eleventh International Congress on Drug Therapy in HIV Infection in Glasgow* had the incidental effect of bringing into question evidence from a previous study that suggested that the NRTI (nucleoside reverse transcriptase inhibitor) drug abacavir was less potent in people starting HIV therapy with high viral loads than another NRTI drug, tenofovir.

**Background – why this may be important**
This new evidence may have considerable importance because it could cause the compilers of treatment guidelines to revise their views on whether abacavir-containing regimens in antiretroviral combination therapy should be rated as equal to tenofovir-based ones, with a number of implications for patient choice and cost.

This year’s *HIV Treatment Guidelines* issued by the British HIV Association (BHIVA) recommended that the best NRTI choice for first-line regimens was tenofovir plus FTC (*Truvada*, or in a triple pill with efavirenz as *Atripla*). They recommended abacavir plus 3TC (*Kivexa*, called *Epzicom* in the US) as an alternative choice, but only for people starting treatment with viral loads below 100,000 copies/ml.

The authors did this after weighing up the evidence from a number of trials, but due to its size the findings from one trial predominated. In this trial, ACTG 5202 (Sax), the time to treatment failure in people taking *Kivexa* who started with high viral loads was significantly shorter than the time in people taking *Truvada*. (ACTG 5202 also compared boosted atazanavir with efavirenz, but found no difference in their efficacy.)

This recommendation in turn gave the appearance of clashing with the prescribing recommendations of the London Specialised Commissioning Group, which issued a strong recommendation to London HIV clinics in April 2011 that they should start a higher proportion of patients on *Kivexa*-based regimens for cost reasons (this shift was achieved and the required savings made, but in fact the majority of London patients still start on *Truvada*).

**What the new studies say**
Findings that abacavir is as potent as tenofovir, at least in some regimens, may therefore be of some importance.

At the Glasgow conference, Joseph Eron of the University of North Carolina compared viral suppression results at 48 weeks in two trials of the new integrase inhibitor dolutegravir. In a trial called *SPRING-2*, presented at the International AIDS Conference in Washington this summer, dolutegravir was as potent as the first-generation integrase inhibitor raltegravir, while in another study called *SINGLE*, presented at the ICAAC conference in September, it proved superior to the standard-of-care drug efavirenz, producing a viral load of under 50 copies/ml in 88% of patients at 48 weeks, compared with 81% on efavirenz.

In *SPRING-2*, doctors chose whether to accompany the integrase inhibitors with either *Kivexa* or *Truvada* while in the *SINGLE* study, participants were randomised either to dolutegravir plus *Kivexa/Epzicom* or to *Atripla*.

In *SINGLE*, the 7% superiority of dolutegravir/abacavir/3TC over *Atripla* appeared to be independent of trial subjects’ initial viral loads. In people with viral loads under 100,000 copies/ml, the respective proportions with viral loads below 50 copies/ml were 90% on dolutegravir/*Kivexa* and 83% on *Atripla*. Viral load suppression rates were lower in people starting treatment with viral loads over 100,000 copies/ml but the 7% superiority margin was unchanged: 83% of dolutegravir/*Kivexa* versus 76% on *Atripla* were virologically suppressed.
The point here is that if abacavir is less potent than tenofovir in people with higher viral loads, one would expect the dolutegravir superiority margin to be smaller in those patients, and it wasn’t. In SPRING-2, it was possible to make a more direct comparison of Kivexa and Truvada in people with high and low viral loads. In people with viral loads under 100,000 copies/ml who took Kivexa, 87% and 88% respectively on dolutegravir and raltegravir achieved undetectable viral loads, and in people who took Truvada 92% and 91% respectively.

In people starting with viral loads over 100,000 copies/ml who took Kivexa, 81% and 82% respectively on dolutegravir and raltegravir achieved undetectable viral loads, and in people who took Truvada 83% and 71% respectively. None of these differences were statistically significant.

Neither of these studies were set up specifically to compare tenofovir-based with abacavir-based regimens. However with 1655 subjects, of whom 495 (30%) had an initial viral load over 100,000 copies/ml, they may be large enough to make HIV specialists re-evaluate the relative potency of abacavir versus tenofovir.

With another meta-analysis being published recently that found no raised rates of heart attack in people taking abacavir in randomised controlled trials (Ding), in contrast to findings in cohort studies, this could also swing the balance of favour back towards the equal recommendation of abacavir and tenofovir in treatment guidelines.

References

Serbia man wins false HIV compensation
By: AFP | November 25, 2012

BELGRADE — A Serbian court has ordered a hospital to pay 4,000 euros ($5,200) in compensation to a man who claimed his life was ruined when he was falsely diagnosed with HIV, a newspaper reported Saturday. Dragisa Zekic was 23 years old when he was diagnosed with HIV in 1986 at the main Serbian hospital in Belgrade, the Vecernje Novosti daily reported. “I went to the hospital with a fever and was dismissed with the HIV diagnosis,” he told the paper. Zekic said a doctor had told him at the time that he had “a month or (up to) six months” to live. After telling his employer of the diagnosis, Zekic was forced to quit his job and was abandoned by friends, he said.

At another job his employers “did everything to keep me out of contact with other employees... before offering me an early retirement for disabled people,” he said. Sixteen years later, in 2002, once HIV tests became widely available and anonymous, Zekic tested himself again and thought it was a mistake when he received a negative result.

“They tested me five times that day and it was always negative,” he said. The court ruling comes at the end of an eight-year long legal process. Zekic said he was only looking for “an apology, because my life was wrongly ruined”. “I did not fight a doctor’s mistake, but against discrimination. I was healthy, but despised and humiliated because everybody thought I was infected” with HIV, he said. Since he found out that his diagnosis was false, the 49-year-old has become involved in organisations fighting discrimination against people with HIV and AIDS. Serbia has officially prohibited bias against HIV-positive people for decades, but in practice they face often brutal discrimination, including by some doctors and nurses.

Ugandan anti-gay bill could be law imminently
ANALYSIS / Refugees urge Canada to put pressure on Uganda to respect gay rights
Andrea Houston / National / Saturday, November 24, 2012

Despite an international outcry, Ugandan parliamentarians are poised to pass a new anti-gay law—dubbed the "Kill the Gays" bill. Ugandan refugees in Canada say the legislation will be a "disaster" for gay Ugandans.

With the passage of the bill, the central African country will step up persecution of lesbian, gay, bisexual and trans people, says Brenda, a refugee from Uganda who attended an emergency meeting of Pride Uganda Nov 20 at the 519 Church Street Community Centre in Toronto. The group gathered to decide how Canada should best respond to the controversial legislation.
In order to protect them, *Xtra* has concealed the identities of the members of *Pride Uganda*, a Toronto-based group of queer refugees and their allies.

Brenda, whose refugee papers are currently being processed, is pleading for Canada to help queer Ugandans who need to escape. She never wants to go back.

“They will hunt down the gay people. They will kill them,” she says. “It will be a disaster. I’m not happy about it. It is really terrible.

“When that bill passes, most people are going to kill themselves because they can’t leave. In Uganda, gay people are always hiding. If they come out, they are always terrorized, always harassed, always hated. . . I’ll tell you the life gay people will lead. It will not be life anymore.”

Homosexuality is already criminalized in the country, but the proposed measure increases the penalties.

The bill is expected to pass easily, possibly as early as next week. It will then be in the hands of the country’s president, Yoweri Museveni, to sign it into law or veto it. If Museveni opts for a veto, the Ugandan Assembly could overturn it.

Tabled by MP David Bahati in 2009, the bill proposes longer jail terms for homosexual acts than already exist, including a life sentence in certain circumstances.

In its original form, those convicted of "aggravated homosexuality" faced the death penalty. The bill defined "aggravated homosexuality" as occurring when one of the participants is a minor, HIV-positive, disabled or a "serial offender."

By late afternoon Nov 23, there was a glimmer of hope. The BBC reported that a committee of Ugandan MPs had decided to drop the death penalty and replace it with life imprisonment. The bill, possibly now with these amendments, heads to final debate in Parliament next week.

Activists in Uganda want the bill scrapped completely. Frank Mugisha, of *Sexual Minorities Uganda (SMUG)*, condemns the bill and warns that, even if amended, gay people would still be at risk of facing the death penalty "in some circumstances."

"Any parent who does not denounce their lesbian daughter or gay son to the authorities would face fines of $2,650 or three years in prison,” he states. "It places a total ban on public discussion of an issue whose existence cannot be wished away."

Martin, coordinator of the emergency Pride Uganda meeting in Toronto, says the bill would prohibit all HIV groups that serve gay people in Uganda. That will have “a disastrous effect on the country’s HIV response, resulting in more HIV infections,” according to the International HIV/AIDS Alliance.

**Members of Pride Uganda on the steps of Toronto's 519 Church Street at an emergency meeting about the "Kill the Gays" bill**

In addition, any of the offences contained in the bill can be applied to a Ugandan citizen who allegedly commits them—even outside the country. Martin says that section is particularly chilling for refugees in Canada who live in fear they may be sent back.

“So, as a gay man living in Canada, I would be breaking this law,” he says. “I hope the Canadian people see how it is affecting Ugandans back home, but I want Canadians to understand how it is affecting those who are here as well."

Canadians can help by writing letters to their MPs, pressuring them to speak out to world leaders. “Whatever the Canadian government can do, please assist us,” Martin says.

The Centre for Inquiry, Canada’s humanist advocacy group, is planning a peaceful protest at the Ugandan High Commission in Ottawa Dec 3. All Out, the international gay rights activist organization, is circulating a petition.

SMUG’s Mugisha is posting frequent updates on his Twitter feed: [@frankmugisha](https://twitter.com/frankmugisha). Canada recently expressed strong criticism to Uganda’s parliamentary speaker, Rebecca Kadaga. At the Inter-Parliamentary Union conference in Quebec City in October, Foreign Affairs Minister John Baird called on Uganda to respect and protect gay people.

Kadaga blasted Baird, accusing him of “forcing the people of Uganda to embrace homosexuality.”

“I was not aware that we had been invited here to promote homosexuality,” she said. Upon returning home, Kadaga promised to push for swift passage of the bill, “as a Christmas gift” to Uganda.

Baird did not respond to *Xtra’s* requests for comment, but his press secretary, Rick Roth, sent a statement. “The Government of Uganda must live up to its international obligations and protect all Ugandans from discrimination and abuse, regardless of sexual orientation.”
Roth also stated that Canadian officials have conveyed Canada's concerns about the bill to Ugandan foreign ministry officials as well as to Uganda’s high commissioner to Canada.

Liberal MP Carolyn Bennett says Baird should have used more “diplomacy” with Kadaga. It’s incredibly frustrating, she says. Many Canadians want the government to speak out and they applauded Baird for finally taking a strong position with Uganda. But Bennett says it seems Canada now shoulders the blame for speeding up the process.

“It’s very upsetting that this fast-tracking of the bill may be in reaction to what happened in Quebec City,” she says. “Diplomacy is supposed to be diplomatic. In many parts of the world, saving face is very important. We’re very, very worried. [Africa] is the next frontier in the GLBT rights movement.”

NDP MP Randall Garrison says Canada should proceed carefully. “We don’t wish to place the LGBT community at further risk in Uganda by precipitous actions.”

Brenda says she’s pleased to see Canadians are talking about this. She hopes to see more leaders offer support. In Uganda, activists take enormous risks in speaking out against the bill because it out them, making them targets. Authorities raid press conferences and activists are terrorized. She says gay people are beaten in the streets daily, lesbians are “correctively raped,” and families are threatened.

“LGBT people are suffering,” she says. “They are in pain and they are crying out.”

Antonin, a refugee from Ghana who came to Canada in July, says he, too, can never go back. His picture and contact information were splashed over several websites after he attended a human rights conference in Geneva last year. That’s when his father tried to poison him.

“He wanted to eliminate me fast. My family completely rejected me,” he says. “With help, I was sent to the UN to save my life . . . When I first saw my picture on the net I wanted to commit suicide. I just wanted to end it.

“When the bill passes in Uganda, gay and lesbian people will live in fear and panic. They will be afraid to go out. And there will be no support for them because even groups that fight for the rights of homosexuals will be shut down. They will be put in prison.”

Another way for Canada to respond would be to open up its borders and make it easier for gay refugees from Uganda to seek asylum here, Garrison says.

“The most urgent thing we can do in Canada is ensure there is a safe haven available for people whose lives are in danger,” he says. “The problem is, the changes that have just been made to Canada’s refugee determination system make it particularly difficult for LGBTQ refugees.”

Refugees now have very short time-lines to put together a case and essentially prove to border officials that they are gay. “These are people who have fled a country where being out is dangerous. So they come here and within 14 days must out themselves to government authorities,” Garrison says.

“[Refugees] have to demonstrate that they are gay after coming from a country where demonstrating that they are gay will subject them to possible violence. That makes it very difficult to substantiate those claims.”

Federal Citizenship and Immigration Minister Jason Kenney did not respond to Xtra’s request for comment.

Liberal immigration critic Kevin Lamoureux, on the other hand, is speaking out against the bill, but he stopped short of calling for Canada to open its borders.

“We are talking about tens of millions of refugees that need asylum in the world,” he says. “In Uganda, we aren’t talking about dozens of people who will be directly affected by this. We are talking about thousands of people.”

He says Canada should continue to react by strongly condemning the bill to other governments around the world. “It’s hard for me to comprehend how, in modern-day society, we could have a country even contemplate legislation of this nature. This is just horrific.”

Many gay Ugandans put the blame squarely on American evangelicals who have been travelling to the African country and spreading negative messages about lesbian, gay, bisexual and trans people. It’s something SMUG’s David Kato tried to warn the world about before he was beaten to death in his home in 2011.

Kato’s name appeared on a list with other gay and lesbian people in a newspaper story under the headline “Hang them!”

At the time, Mugisha told the press, “The blood of David is on the hands of American preachers who came to Uganda. They share much of the blame for presenting us as less than human.”

Martin says American evangelicals remain the driving force behind the push for the bill’s speedy passage. “The church is working against the LGBT community.”
This will have a ripple effect throughout all of Africa, he says. “Other African countries are looking at what goes on in Uganda and trying to model after that.”

Most countries in Africa are intensely homophobic, Antonin says. Uganda is certainly not alone. “There is an attack every day... In Nigeria, there is a similar ‘Jail the Gays’ law before Parliament. Look at Zimbabwe. Then there’s the North African Arab countries; those are very severe. Tunisia, Egypt, Libya, they have laws against homophobia, [punishable] by killing and hanging.”

Antonin is urging Canada to pressure all countries in Africa to respect gay rights. “Talk to the key leaders in these countries. Tell them homosexuals are not evil. We are not outcasts. We are not criminals. We are part of society.”

Cellphones Reshape Prostitution in India, and Complicate Efforts to Prevent AIDS
Kuni Takahashi for The New York Times

By Gardiner Harris

MUMBAI, India — Millions once bought sex in the narrow alleys of Kamathipura, a vast red-light district here. But prostitutes with inexpensive mobile phones are luring customers elsewhere, and that is endangering the astonishing progress India has made against AIDS.

Indeed, the recent closings of hundreds of ancient brothels, while something of an economic victory for prostitutes, may one day cost them, and many others, their lives.

“The place where sex happens turns out to be an important H.I.V. prevention point,” said Saggurti Niranjan, program associate of the Population Council. “And when we don’t know where that is, we can’t help stop the transmission.”

Cellphones, those tiny gateways to modernity, have recently allowed prostitutes to shed the shackles of brothel madams and strike out on their own. But that independence has made prostitutes far harder for government and safe-sex counselors to trace. And without the advice and free condoms those counselors provide, prostitutes and their customers are returning to dangerous ways.

Studies show that prostitutes who rely on cellphones are more susceptible to H.I.V. because they are far less likely than their brothel-based peers to require their clients to wear condoms.

In interviews, prostitutes said they had surrendered some control in the bedroom in exchange for far more control over their incomes.

“Now, I get the full cash in my hand before we start,” said Neelan, a prostitute with four children whose side business in sex work is unknown to her husband and neighbors. (Neelan is a professional name, not her real one.)

“Earlier, if the customer got scared and didn’t go all the way, the madam might not charge the full amount,” she explained. “But if they back out now, I say that I have removed all my clothes and am going to keep the money.”

India has been the world’s most surprising AIDS success story. Though infections did not appear in India until 1986, many predicted the nation would soon become the epidemic’s focal point. In 2002, the C.I.A.’s National Intelligence Council predicted that India would have as many as 25 million AIDS cases by 2010. Instead, India now has about 1.5 million.

An important reason the disease never took extensive hold in India is that most women here have fewer sexual partners than in many other developing countries. Just as important was an intensive effort underwritten by the World Bank and the Bill and Melinda Gates Foundation to target high-risk groups like prostitutes, gay men and intravenous drug users.

But the Gates Foundation is now largely ending its oversight and support for AIDS prevention in India, just as efforts directed at prostitutes are becoming much more difficult. Experts say it is too early to identify how much H.I.V. infections might rise.

“Nowadays, the mobility of sex workers is huge, and contacting them is very difficult,” said Ashok Alexander, the former director in India of the Gates Foundation. “It’s a totally different challenge, and the strategies will also have to change.”

An example of the strategies that had been working can be found in Delhi’s red-light district on Garstin Bastion Road near the old Delhi railway station, where brothels have thrived since the 16th century. A walk through dark alleys, past blind beggars and up narrow, steep and deeply worn stone staircases brings customers into brightly lighted rooms teeming with scores of women brushing each other’s hair, trying on new dresses, eating snacks, performing the latest Bollywood dances, tending small children and disappearing into tiny bedrooms with nervous men who come out moments later buttoning their trousers.
A 2009 government survey found 2,000 prostitutes at Garstin Bastion (also known as G. B.) Road who served about 8,000 men a day. The government estimated that if it could deliver as many as 320,000 free condoms each month and train dozens of prostitutes to counsel safe-sex practices to their peers, AIDS infections could be significantly reduced. Instead of broadcasting safe-sex messages across the country — an expensive and inefficient strategy commonly employed in much of the world — it encircled Garstin Bastion with a firebreak of posters with messages like “Don’t take a risk, use a condom” and “When a condom is in, risk is out.”

Surprising many international AIDS experts, these and related tactics worked. Studies showed that condom use among clients of prostitutes soared.

“To the credit of the Indian strategists, their focus on these high-risk groups paid off,” said Dr. Peter Piot, the former executive director of U.N.AIDS and now director of the London School of Hygiene and Tropical Medicine. A number of other countries, following India’s example, have achieved impressive results over the past decade as well, according to the latest United Nations report, which was released last week.

But now that mobile phones are untethering prostitution from brothels, those targeted measures are threatened. At the same time, the advent of cellphones seems to be expanding the sex marketplace — luring more women into part-time sex work and persuading more men to pay for sex. Cellphone-based massage and escort services are mushrooming across India.

“There may now be clients who may not have otherwise availed themselves of the services but do so now because it is easier and more private,” said Suneeta Krishnan, a senior epidemiologist with Research Triangle Institute of North Carolina.

The changes have led to a steep drop in business on Delhi’s Garstin Bastion Road and have nearly destroyed Mumbai’s Kamathipura district, where brothels had thrived since the 18th century.

Champa, a wrinkled madam with silver toe rings, bangles on her wrists and henna-dyed hair, has for 50 years owned a brothel in a narrow lane here. But like many other industries where information technology has undermined the role of middlemen between buyers and sellers, Champa’s business is withering.

“It’s the end of Kamathipura,” Champa said with a resigned wave as she squatted on the floor of her entryway.

She once had as many as 20 prostitutes living in her nine-bedroom brothel; she now has three, she said. Worse, at least from her point of view, the women working for her collect their own fees and offer her just $2 a day to rent one of her tiny bedrooms. As recently as five years ago, Champa — she has just one name — collected $2 for every client served.

As Champa spoke, several garishly dressed young women walked through the brothel’s tiny foyer to sweep and water the hard dirt floor just outside. The lane was teeming with laborers, uniformed schoolchildren, and veiled matrons. The prostitutes soon settled onto benches and teased the men getting haircuts at a nearby outdoor barbershop.

There were once 75 brothels on this lane; now there are eight. Kamathipura had as many as 50,000 prostitutes in the 1990s but now has fewer than 5,000, according to city officials and nongovernmental organizations.

Kamathipura’s destruction is partly a tale of urban renewal. India’s rapid development has turned former slums into sought-after addresses, and rising land values led many brothel owners to sell out.

But just as important has been the spread of cellphones into the hands of nearly three out of four Indians. Five years ago, cellphones were still a middle-class accouterment. Fierce competition led prices to plunge, and now even trash pickers and rickshaw drivers answer pocket phones.

But not all has changed. Vicious madams still exist, human trafficking is still rampant, village girls are still duped into the trade, and some brothels still thrive. Most prostitutes are illiterate, come from lower castes and are poor. But cellphones have given them a measure of power they did not have before.

“I’m happy that mobile phones are so popular and that I have this opportunity," said Kushi, a mother who got into secret, part-time prostitution after she left her abusive and alcoholic husband. (Kushi is her work name.) She has three to four clients a week and charges each about $20, she said, compared with a typical price of $4 in cheap brothels.

“Cellphones allow the women to keep much more of their money,” Mr. Niranjan of the Population Council said. “But they make H.I.V. prevention programs more challenging.”
Can Asia save Africa from drug-resistant malaria?

By Jonah Fisher BBC News, Sai Yok, Thailand

In a wooden hut on the Thai-Burmese border, a community health worker pricks the finger of six-month-old Tannakorn, who lets out a whimper.

Fifteen minutes and a blood test later, his mother is given good news. Tannakorn's fever is not malaria and he can go home.

It is an unremarkable exchange, repeated thousands of times every day in South East Asia and around the world.

But in the last year, the work of this clinic in Sai Yok district and those nearby have assumed an importance that goes far beyond the local.

This is now the frontline in the fight to stop South East Asia's drug-resistant malaria going global.

Earlier this year, scientists announced that strains of malaria that resisted the most widely-used treatment had been confirmed in two locations in South East Asia.

One has been known about since 2006, straddling Cambodia and eastern Thailand. The other, newly verified, was in the west where the mountains of Burma and Thailand join.

The news sent a shudder through international agencies leading the fight against the disease.

Since 2003 the amount of money spent tackling malaria has risen more than eight-fold. The multi-billion-dollar campaign is acknowledged as one of the world's public health success stories.

The funding increase, largely through the Global Fund to Fight AIDS, Tuberculosis and Malaria, the use of bed nets, rapid test kits and effective treatment have led to a steady fall in the number of people both infected and dying. Some estimate that more than 750,000 lives have been saved.

In Africa, which accounts for 90% of the world's malaria fatalities, the number dying each year has dropped by a third and talk had begun to turn to the possibility of totally eradicating malaria by 2015.

For the last 15 years, the most effective and widespread drugs used against malaria have been derived from a Chinese plant, artemisia annua.

When used quickly and effectively, artemisinin-based combination therapy (ACT) as it is known, has proved highly effective in clearing the bloodstream of the plasmodium falciparum parasite that cause most cases of malaria—usually within three days.

Stopping drug resistance spreading means monitoring those who have been treated, and hitting any parasites that survive with a second line of treatment before they are passed on to others.

**Financial incentive**

In rural Thailand, where many walk for miles to reach the clinic, getting people to return for follow-up tests has not been straightforward.

But thanks to increased interest and international money, Witthaya Saipomsud, who oversees many of Sai Yok's clinics, has since February been able to offer a financial incentive.

If a malaria patient completes a series of blood tests up to 28 days after the first treatment, they get 1,000 baht ($30, £18.70).

"We have a highly effective drug to treat malaria and we need to protect it because there is no new drug available on the market," Dr Fatoumata Nafo-Traore Roll Back Malaria says.

"We did follow up tests on 190 of our Falaciparum malaria patients this year. After 28 days, 40 still had malaria parasites," Mr Saipomsud says.

It is a worrying drop in the effectiveness of the artemisinin-based drugs, and with 40% of the patients coming from Burma, a worrying snapshot of the situation there.

Thanks to the efforts of health workers like Mr Saipomsud, and the widespread availability of treatment, malaria still only kills a handful of people in Thailand each year.

What is a huge headache for other parts of the world is merely a nagging pain for the Thai medical system.

"We are mostly concerned with injuries caused by accidents and cancer here," Somchai Wititanan, director of Sai Yok's hospital, says with a wry smile. "Malaria is not a scary disease because if you get the treatment, you survive."

In the last year, he says 200 malaria cases have been admitted to his hospital, with 12 showing signs of drug resistance.

All were sent to Bangkok, where a second line of treatment usually involving quinine administered intravenously proved effective.

'Massive crisis'
How drug resistance develops

- Natural selection—a mutant parasite will survive treatment and reproduce
- Prevalence of fake and substandard drugs allow tolerance to develop
- Use of single drug as treatment instead of combination
- Patients failing to complete the full course of medicine

The nightmare scenario, however, is a repeat of what took place in the 1980s, with what was then the most commonly used anti-malarial drug, chloroquine.

Resistance to chloroquine emerged in South East Asia, spread, and when it reached Africa, the number of malaria cases rose sharply.

Estimates for the number who died vary widely, but in many of the areas surveyed, the number of child fatalities from malaria more than doubled.

The focus now is on trying to monitor and contain artemisinin drug resistance into a few hotspots, prolonging the drug’s effective lifespan globally until alternative treatments are available. Africa’s hopes of maintaining its progress rests firmly on South East Asia’s efforts.

"In Africa [if resistance spreads], we’d see more cases and we’d see more deaths," says Dr Fatoumata Nafo-Traore, former health minister of Mali, and now executive director of Roll Back Malaria, an alliance of global groups.

"We have a highly effective drug to treat malaria and we need to protect it because there is no new drug available on the market."

Resistance to artemisinin-based drugs reaching Africa would be a "massive crisis", she said.

The success at containing the spread of the resistance may depend on what is taking place in Burma.

It has the most malaria cases in Asia, and with the healthcare system threadbare, it is ill-equipped to introduce systems for monitoring and containment. Burma’s highly mobile migrant population may already be spreading the drug-resistant strain around the world.

"Our country is the gateway for this kind of drug-resistant malaria to spread west to Bangladesh and India," Saw Lwin, from Burma’s Health Ministry, told reporters in Thailand.

"If we cannot contain it at the source, this is a global threat."

The earliest new drugs are likely to be available is 2015, with considerable excitement surrounding the possible development of malaria vaccines.

For now, in the rural clinics of Thailand, Cambodia and Burma, health workers are fighting to defend one of the pillars that support a global success story.

Short DNA Strands in Genome May Be Key to Understanding Human Cognition and Diseases

ScienceDaily (Nov. 21, 2012) — Short snippets of DNA found in human brain tissue provide new insight into human cognitive function and risk for developing certain neurological diseases, according to researchers from the Departments of Psychiatry and Neuroscience at Mount Sinai School of Medicine.

The findings are published in the November 20th issue of PLoS Biology.

There are nearly 40 million positions in the human genome with DNA sequences that are different than those in non-human primates, making the task of learning which are important and which are inconsequential a challenge for scientists. Rather than comparing these sequences strand by strand, Schahram Akbarian, MD, PhD, Professor of Psychiatry and Neuroscience at Mount Sinai School of Medicine, wanted to identify the crucial set of differences between the two genomes by looking more broadly at the chromatin, the structure that packages the DNA and controls how it is expressed.

They found hundreds of regions throughout the human genome which showed a markedly different chromatin structure in neurons in the prefrontal cortex, a brain region that controls complex emotional and cognitive behavior, compared to non-human primates. The findings of the study provide important insights for diseases that are unique to humans such as Alzheimer’s disease and autism.

"While mapping the human genome has taught us a great deal about human biology, the emerging field of epigenomics may help us identify previously overlooked or discarded sequences that are key to understanding disease," said Dr. Akbarian. "We identified hundreds of loci that represent untapped areas of study that may have therapeutic potential."

Dr. Akbarian and his research team isolated small snippets of chromatin fibers from the prefrontal cortex. Next, they analyzed these snippets to determine what genetic signals they were expressing. Many of the sequences with human-specific epigenetic characteristics were, until recently, considered to be "junk DNA" with no particular function.
Now, they present new leads on how the human brain has evolved, and a starting point for studying neurological diseases. For example, the sequence of DPP10—a gene critically important for normal human brain development—not only showed distinct human-specific chromatin structures different from other primate brains such as the chimpanzee or the macaque, but the underlying DNA sequence showed some interesting differences from two extinct primates—the Neanderthal and Denisovan, most closely related to our own species and also referred to as ‘archaic hominins’.

"Many neurological disorders are unique to human and are very hard as a clinical syndrome to study in animals, such as Alzheimer’s disease, autism, and depression," said Dr. Akbarian. "By studying epigenetics we can learn more about those unique pieces of the human genome."

The research team also discovered that several of these chromatin regions appear to physically interact with each other inside the cell nucleus, despite being separated by hundreds of thousands of DNA strands on the genome. This phenomenon of "chromatin looping" appears to control the expression of neighboring genes, including several with a critical role for human brain development.

"There is growing consensus among genome researchers that much of what was previously considered as ‘junk sequences’ in our genomes indeed could play some sort of regulatory role," said Dr. Akbarian. This study was supported by grants from the National Institutes of Health. Dr. Akbarian plans to do more epigenetic studies in other areas of the brain to see if there are additional chromatin regions that are unique to humans. They also plan to study the epigenomes of other mammals with highly evolved social behaviors such as elephants.

**Journal Reference:**

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**The Evolution of Mutualism in Gut Microbiota Via Host Epithelial Selection**

**Abstract**

The human gut harbours a large and genetically diverse population of symbiotic microbes that both feed and protect the host. Evolutionary theory, however, predicts that such genetic diversity can destabilise mutualistic partnerships. How then can the mutualism of the human microbiota be explained? Here we develop an individual-based model of host-associated microbial communities. We first demonstrate the fundamental problem faced by a host: The presence of a genetically diverse microbiota leads to the dominance of the fastest growing microbes instead of the microbes that are most beneficial to the host.

We next investigate the potential for host secretions to influence the microbiota. This reveals that the epithelium–microbiota interface acts as a selectivity amplifier: Modest amounts of moderately selective epithelial secretions cause a complete shift in the strains growing at the epithelial surface. This occurs because of the physical structure of the epithelium–microbiota interface: Epithelial secretions have effects that permeate upwards through the whole microbial community, while lumen compounds preferentially affect cells that are soon to slough off. Finally, our model predicts that while antimicrobial secretion can promote host epithelial selection, epithelial nutrient secretion will often be key to host selection. Our findings are consistent with a growing number of empirical papers that indicate an influence of host factors upon microbiota, including growth-promoting glycoconjugates. We argue that host selection is likely to be a key mechanism in the stabilisation of the mutualism between a host and its microbiota.

**Author Summary**

The cells of our bodies are greatly outnumbered by the bacteria that live on us and, in particular, in our gut. It is now clear that many gut bacteria are highly beneficial, protecting us from pathogens and helping us with digestion. But what prevents beneficial bacteria from going bad? Why don’t bacteria evolve to shirk on the help that they provide and simply use us as a food source? Here we explore this problem using a computer model that reduces the problem to its key elements. We first illustrate the basic problem faced by a host: Whenever beneficial bacteria grow slowly, the host will lose them to fast-growing species that provide no benefit. We then propose a solution to the host’s problem: The host can use secretions—nutrients and toxins—to control the bacteria that grow on the epithelial cell layer of the gut. In particular, our model predicts that the epithelial surface acts as a “selectivity amplifier”. The host can thereby maintain beneficial bacteria with only small amounts of weakly selective secretions. Our model fits with a growing body of experimental data showing that hosts have diverse and important influences on their gut bacteria.
HIV/AIDS: The female condom showdown

JOHANNESBURG, 30 November 2012 (PlusNews) – Introduced more than 15 years ago, the female condom has gotten a bad rap, with some comparing it to having sex with a plastic bag, while many others still don’t know about the only female-controlled HIV prevention method available.

Its uptake and distribution have been outpaced by traditional male condoms: according to a recent UNAIDS report, only one donor-funded female condom was available for every 10 women of reproductive age in sub-Saharan Africa last year. Even male condom distribution stood at a paltry nine per every man of the same age in the region.

As new versions of the female condom, or femidom, continue to be developed, IRIN/PlusNews asked one couple to test the newer FC2 female condom, which is said to be quieter and less expensive to produce than the original FC1 female condom, and its newer rival, the Chinese-produced Cupid. The two products are the only female condoms that have been prequalified by the World Health Organization. Prequalification is a service provided by the global health body to test the safety, quality and efficacy of medicinal products before they are released to the public.

She said

"I’d only ever used a female condom once. I remember application being tricky, awkward and involving something akin to the one-legged perching stance you assume when you first start using tampons as a girl—when the idea of having to stick your fingers up ‘there’ is simultaneously weird, gross and frightening. You imagine trips to the emergency room in some horribly embarrassing scene and having to admit to a nurse that you got it all wrong and need help to correct ‘the situation’.

“This time, I was pleasantly surprised. Application times for both the FC2 and the Cupid were roughly the same, and nearly equal to the time it takes to put on a male condom, but not without some serious preparation.

“The FC2 has six, relatively easy steps. The best part: there are pictures, which makes everything easier... But packed onto half of the Cupid’s purple, hulking pack are no fewer than 10 steps. Each step is explained in anywhere from two to four lines, accompanied by an itsy-bitsy picture, which in some cases also contains text you’d need a magnifying glass to read. Before using the Cupid, I took about five minutes to study the packet—after literally having to find my glasses. I put them on the bedside table by the Cupid in case I needed a quick refresher before use.

“Actually inserting the Cupid was intimidating. This new version features a new circular sponge at the end, about the size of the top of a cool drink can. Intimidating doesn’t cover it. Actually, when we pulled it out, my partner actually said, ‘Whoa, that is not attractive,’ which is always what a girl wants to hear in compromising positions... I felt like my face was frozen in a really attractive ‘am I doing this right?’ look.

“I took a brief second to wonder how you’d pack more than one Cupid into your handbag—the thing is huge. I actually laughed out loud upon its removal because it looked like a really tiny flotation device.

“To be honest though, once the Cupid was where it was supposed to be, it was leagues above the FC2 in feeling. But I couldn’t help focusing on making sure either femidom was where it should be during sex. I figure this is something you’d get over with practice, but it didn’t inspire a lot of position changes. And neither is it especially pretty—there’s still the outer ring hanging about—but it was still a far cry from a plastic shopping bag. There, I said it.

“My verdict: I still prefer traditional condoms, but then again, I don’t have to argue about condom use with my partner. Lucky girl.”

He said

“I was initially excited by trying out a new form of contraception, but with some heavy scepticism. The original was awkward to put on, and it’s a bit anxiety provoking because you don’t have the control you have with a male condom, which fits better to the body. Actually, it’s kind of scary in that way, even though you know they’re effective.

“With both condoms, it felt like there was more room for error than with male condoms. We read with the Cupid that you have to be careful about the penis going between the condom and the vagina. It makes me wonder if you could also have that problem with the original.

“Although the FC2 looks a lot better than the Cupid, it feels like FC2 skimps on lube. It’s really dry and because of that, it sticks to you the whole time. It kind feels like you’re having sex with a glove—not that I know what that feels like.
“With the Cupid, in some ways you feel freer as a guy, without having something strapped to your penis. You might have a bit more freedom—being a man—with the feeling of the female condom, but you have more freedom to do stuff like change positions when wearing the male condom.”

“I couldn’t feel the sponge [of the Cupid]. I know people have said it’s supposed to add something in terms of feeling, but I’m not 100 percent convinced.

The verdict
“We’d pick the Cupid over the FC2 any day, but won’t be moving to female condoms any time soon. Well, if we could even find them.”

Should Everyone HIV+ Be Required to Disclose That to Every Sexual Partner?
By John-Manuel Andriote

Forty-five U.S. states have made failure to do so a criminal offense. Two-thirds of HIV-positive adults are not aware of that.

"HIV criminalization is the biggest driver of stigma in our society," said Sean Strub, the HIV-positive founder of the SERO Project, a non-profit human rights organization combating HIV-related stigma by conducting original research, briefings, forums and meetings around the country aimed at ending inappropriate criminal prosecutions of people with HIV.

"After all," said Strub, "what is more stigmatizing than when the government enshrines criminalization in the law, making different laws for different groups of people based on an immutable characteristic" such as HIV infection? The result, he said, is the creation of "a viral underclass of persons with rights inferior to others, especially in regard to their sexual expression."

Consider Nick Rhoades, an HIV-positive gay man in Iowa, going about his life. Faithful adherence to his medications rendered Rhoades' HIV infection undetectable. Studies indicate those with undetectable virus are up to 96 percent less likely to transmit the virus to someone else. Rhoades arranged a sexual encounter with a man he met online. Neither of them spoke about HIV.

When a friend later told the other man that Rhoades was HIV-positive, the man went to the county prosecutor and pressed charges. Despite the fact that Rhoades used a condom, had an undetectable viral load, and did not transmit the virus, he was sentenced to 25 years in prison for not disclosing his HIV status. After a year, the judge reconsidered Rhoades' sentence and released him—but still required him to register as a sex offender for the rest of his life.

HIV-specific criminal laws in about two-thirds of U.S. states mean people with HIV are potentially subject to prosecution for not disclosing their HIV status, while 45 states have specific laws about sexual relationships. Other states do not have HIV-specific statutes, but a positive person can still be prosecuted under general criminal statutes. To date, HIV-specific criminal charges have been filed more than 1,000 times in the United States alone.

These laws undermine public health efforts to identify those with HIV and get them into treatment, and thus to greatly lower their risk of infecting anyone else. A 2012 SERO Project survey of 2,076 HIV-positive Americans found that, especially in the Midwest, nearly half of respondents felt it was reasonable to avoid HIV testing—40 percent said the same about avoiding medical care—because of fear of prosecution.

The survey also found that nearly two-thirds of respondents weren't aware of the laws in their states requiring (or not) HIV-positive people to disclose their status before having sex with someone. Even fewer were clear about what behaviors put them at risk for arrest in their state. Although 58.9 percent believed it was ethical or morally right to disclose their status, more than 8 in 10 respondents believed that both sexual partners share equally in the responsibility for safer sex, a view in line with the usually accepted understanding of individual responsibility and consensual sex between adults.

"Criminalizing the sexual conduct of those living with HIV is justified only when there is evidence that an individual intended to harm another person," said Strub. "Prosecutions in these instances should focus on the proof of intent to harm and the resulting injury."

Without this specificity, Strub added, laws criminalizing HIV "perpetuate the persistent public perception that those with HIV, solely by virtue of their infection with HIV, are inherently dangerous and pose a unique and significant risk to the community."

This article available online at:
More infectious HIV strains spreading in India
Archita Bhatta
30 November 2012 | EN

[new delhi] Indian scientists have found new strains of the HIV-1-C subtype – which is responsible for half of the world’s HIV infections – are evolving rapidly in this country.

The proportion of some of these new strains of the HIV-1 subtype went up from two per cent in 2000–2003 to 30 per cent a decade later, said their study, published in the Journal of Biological Chemistry this month (6 November). The HIV-1-C accounts for more than 95 per cent of infections in India.

This is for the first time that scientists have shown that HIV-1-C, considered stable since its detection in early 1980s, is evolving.

The scientists, led by Udaykumar Ranga, professor of molecular biology and genetics at the Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bangalore, have identified five different strains of HIV-1-C. Of these, one strain was found to be more infectious than others.

For their study, the scientists used blood samples collected from diverse hospitals and research institutes in Bangalore, Chennai and New Delhi.

What helps the HIV virus infect human beings is a protein called NF-kappaB. While other HIV strains have one or two copies of NF-kappaB, the conventional HIV-1-C subtype has three copies, which explains its higher prevalence all over the world.

Significantly, the JNCASR scientists found the more infectious of the new strains to have as many as four copies of NF-kappaB – though they were not more virulent than the original strain. "Our data do not suggest that the new viruses promote faster disease progression to AIDS," Ranga told SciDev.Net.

According to Ranga, no change in disease management strategy is indicated. "The old and new viruses share the same reverse transcriptase gene, hence, the new viral strains must be as sensitive to anti-retroviral therapy as the old viral strains are."

Retroviruses reproduce by transcribing their ribonucleic acid (RNA) into deoxyribonucleic acid (DNA), using the reverse transcriptase enzyme. The resultant DNA inserts itself into host cell DNA and is reproduced along with the cell and its daughters.

Shahid Jameel, group leader for virology, International Centre for Genetic Engineering and Biotechnology, New Delhi, said that the molecular features of their genome do make HIV viruses replicate better, leading to greater transmission.

"But then, now there is more awareness and better anti-HIV drug availability that will counter increased transmission potential," Jameel told SciDev.Net.

More Widespread HIV Treatment Helped South Africa Increase Life Expectancy, Researchers Say

With the average life expectancy for South Africans at 60 years old, the country "has achieved a 'stunning' increase in life expectancy in the last three years due to a government push to roll out antiretroviral drugs (ARVs) to people with HIV/AIDS," according to a study (.pdf) published in the Lancet on Thursday, Reuters reports. Nearly two million of the six million people in the country living with HIV/AIDS are on antiretroviral treatment, compared with only 912,000 in 2009 when the life expectancy was 56.5 years, the news agency notes, adding that the country's treatment program is the largest in the world.

Professor Salim Abdool Karim, director of the Centre for the AIDS Programme of Research and a member of the research team, said, "That increase in life expectancy is nothing short of stunning. You don't see those kinds of increases in the real world," according to Reuters. Lead researcher Bongani Mayosi of the University of Cape Town credited the administration of President Jacob Zuma, including Health Minister Aaron Motsoaledi, for helping to put in place policies allowing for the progress, the news agency states (Sulaiman, 11/29). In related news, "South Africa on Thursday awarded a $667 million contract to supply life-prolonging HIV medicine to 12 international and domestic firms," Reuters reports in a separate article. The firms will share the contract, which "aims to increase the number of people on treatment by nearly 50 percent, to 2.5 million next year," the news agency writes (Motsoeneng, 11/29).

Emerging Vector-Borne Diseases Create New Public Health Challenges

ScienceDaily (Nov. 30, 2012) — West Nile virus, Lyme disease, dengue fever, and plague are examples of "vector-borne zoonotic diseases," caused by pathogens that naturally infect wildlife and are transmitted to humans by vectors such as mosquitoes or ticks.
According to Marm Kilpatrick, who studies the ecology of infectious diseases at the University of California, Santa Cruz, a broad range of human activities can affect the spread of zoonotic diseases. In an article in the December 1 issue of the British medical journal *Lancet*, Kilpatrick and coauthor Sarah Randolph of the University of Oxford describe how widespread land-use change, globalization of trade and travel, and social upheaval are driving the emergence of zoonotic vector-borne diseases around the world. The article is part of a special series of papers focused on emerging zoonotic diseases.

"This collection of papers offers a bridge between ecologists and clinicians whose combined efforts are needed to address the ongoing challenges of emerging zoonotic diseases," said Kilpatrick, an assistant professor of ecology and evolutionary biology at UC Santa Cruz.

Emerging infectious diseases can be roughly split between introduced and locally emerging diseases. Introduced diseases arise from the spread of a pathogen to a new location, as when West Nile virus arrived in New York in 1999 and subsequently spread across North America. Locally emerging diseases increase in importance in areas where they are endemic, as with Lyme disease in the United States over the past three decades. These two types of emerging diseases can differ markedly with respect to infection dynamics, or the number of cases over time, Kilpatrick said.

"Introduced diseases often cause a big spike in infections and then decrease substantially. Locally emerging diseases often show a steady, sustained increase," he said.

The movement of pathogens by global trade and travel results in the emergence of diseases in new regions. Once established, introduced pathogens often evolve to take advantage of their new environment, including new hosts and vectors. With so much of the landscape shaped by human activities, pathogens may thrive by infecting hosts and vectors that do well in human-made environments.

"Increasing human population and the urbanization and agricultural intensification of landscapes puts strong selective pressure on vector-borne pathogens to infect humans and be transmitted by vectors and hosts that live around humans," Kilpatrick said.

Emergence of endemic vector-borne diseases can result from changes in land use, such as expansion of people into new habitats, or environmental changes affecting the wild animals that serve as natural hosts or the insect vectors that spread the disease to humans. Although vector-borne diseases are highly sensitive to climate, climate change does not appear to be a major driving force behind emerging diseases, the authors said.

"So far, climate change has been a relatively minor player compared to land use and socioeconomic factors in the emergence of vector-borne disease," Kilpatrick said.

Social and economic changes, ranging from economic downturns to displacement of populations by armed conflict, frequently precipitate disease outbreaks through their impacts on public health systems, sanitation systems, behavioral patterns, and uses of natural environmental resources. One example cited in the article is a large upsurge of tick-borne encephalitis after an economic downturn in eastern Europe resulted in more people harvesting food from forests.

The incidence of any vector-borne disease involves a complex interplay of multiple factors affecting animal hosts, vectors, and people. Kilpatrick and Randolph emphasize that control of these diseases requires combined efforts by clinicians and public health officials to treat patients, promote behavior likely to minimize the risk of infection, and advise on efforts to reverse the ecological drivers of transmission through vector control, urban planning, and ecological restoration.


"Humans are altering the environment and moving themselves and other organisms around the globe at an ever-increasing pace," said Sam Scheiner, program director for the Ecology and Evolution of Infectious Diseases program at the National Science Foundation (NSF), a joint effort with the National Institutes of Health (NIH). "That has led to a growing disease threat. These papers show how and why that's happening, and what we need to know to ease the disease burden."

**Journal Reference:**

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Exposing the Achilles’ Heel of the AIDS Virus ****

ScienceDaily (Nov. 30, 2012) — Beatriz Apellaniz, PhD holder of the UPV/EHU-University of the Basque Country, has studied in her PhD thesis HIV regions that could be used to design a vaccine. The researcher has focussed her research on a specific region of the surface protein of the Human Immunodeficiency
Virus (HIV), which is responsible for the Autoimmune Deficiency Syndrome (AIDS), one of the diseases with the greatest human morbidity and mortality.

This region, known as the MPER (Membrane-proximal External Region) is one of the domains that is responsible for the fusion of the virus with the cell that it is going to affect, and it is of particular interest, since, as Doctor Apellaniz explains, there are known to be infected people whose immune systems are capable of generating antibodies that target this region in particular. It has been demonstrated that these antibodies could halt the infection in its early stages, which is what a preventive vaccine is seeking to do.

Apellaniz adds that it is a region that does not mutate easily: "Although HIV mutates very quickly, this specific region is very well preserved, so it is a good starting point for designing vaccines or treatments that would not become less effective as HIV goes on mutating."

So the thesis Functional and structural characterization of peptides derived from HIV-1 gp41 membrane-proximal and transmembrane domains. Implications for anti-HIV inhibitor and immunogen development has set out to characterise the MPER and to study a way of inhibiting it, and thus prevent the virus from penetrating the cell it was intending to infect, or to imitate it in order to trigger the generation of antibodies by the immune system. This strategy is known as reverse vaccinology and consists of studying, on a molecular level, which regions and structures recognise the antibodies in the virus before going on to design a vaccine that can trigger the generation of various neutralising antibodies in all individuals.

The cholesterol percentage, one of the keys
Although cholesterol is not a very popular molecule for those people who have elevated cholesterol, it is essential for the organism and, in this case, is one of the keys in the research carried out by Apellániz.

In fact, the amount of cholesterol in the membrane of the virus is extremely high and the MPER is found in this cholesterol-rich membrane. As the researcher herself points out, "according to laboratory work done previously and one of the conclusions of the study, cholesterol is needed in the membrane so that this HIV region can position itself in a specific way to favour the generation of neutralising antibodies. So a possible vaccine that we are proposing in the laboratory would be one that includes the MPER in membranes with a high cholesterol content. In fact, depending on the lipid composition, this HIV region is inserted into the membrane to a greater or lesser extent and adopts different structures. If for example a lot is inserted, it may remain hidden and the antibodies may not recognise it. That is why we are trying to find a way of making this region more exposed."

So the researcher has discovered that a high concentration of cholesterol encourages the MPER to remain exposed and allows a response to be made by the immune system. Apart from that, Apellaniz has pointed out that the characterisation of the lipid composition is also useful in the design of drugs that stop the virus infecting the cell by inhibiting the union of the MPER with the membrane.

These studies, which have led to the publication of seven papers in journals with a high international impact, have been carried out using models that imitate the membrane of the virus, and using the peptides developed and the lipids selected they have immunised rabbits which have generated neutralising immune responses. So the author has concluded that "with some variation, this region would constitute a potential bull's-eye for the development of vaccines."

Bacteria Hijack Host Cell Process, Create Their Own Food Supply to Become Infectious

ScienceDaily (Nov. 29, 2012) — Bacteria that cause the tick-borne disease anaplasmosis in humans create their own food supply by hijacking a process in host cells that normally should help kill the pathogenic bugs, scientists have found.

This bacterium, Anaplasma phagocytophilum (Ap), secretes a protein that can start this process. The protein binds with another protein produced by white blood cells, and that connection creates compartments that siphon host-cell nutrients to feed the bacteria, enabling their growth inside the white blood cells.

The finding defies conventional wisdom about most bacteria, which try to avoid this cellular process. Called autophagy, the process allows a cell to digest parts of itself to produce energy when it is experiencing starvation. But that digestive feature also is enacted by the immune system to help clear away certain intracellular pathogens, including those that cause salmonellosis or shigellosis.

The Ap bacterium, however, launches and then manipulates the autophagy process to its own advantage.
"This study shows how bacteria subvert natural processes," said Yasuko Rikihisa, professor of veterinary biosciences at Ohio State University and lead author of the research. "They are creating their own food supply through a cellular mechanism that hurts other infectious bacteria. And because this process doesn't cause inflammation, they do it very gently, becoming an insider that eventually kills the host cell."

The finding could help identify new targets for drugs to treat this infection, which is a rare but emerging infectious disease that can be lethal for the elderly and people with compromised immune systems. The current first-line treatment is the antibiotic doxycycline.

Also known as human granulocytic anaplasmosis, the disease affects more than 1,000 people per year in the United States, up from just 348 reported cases in 2003, according to the Centers for Disease Control and Prevention. It is transmitted to humans by tick bites primarily from the black-legged tick and the western black-legged tick.

The study appears online this week in the early edition of the Proceedings of the National Academy of Sciences.

The Ap bacterium secretes substances to perform a process resembling mating to infect host cells, primarily the granulocyte class of white blood cells that fight off invading pathogens. Rikihisa's lab previously identified a protein called Ats-1 that is secreted by Ap bacteria during this process.

In this new study, the researchers found that once inside the host cells, Ats-1 binds to another protein called Beclin 1, which is part of a system of molecules involved in the earliest stages of the autophagy process.

The scientists observed that when the two proteins bind, they create little bubbles known as vesicles. Through a series of experiments, the researchers determined that these bubbles were in fact autophagosomes—bubble-like compartments that are formed as a cell prepares to undergo autophagy.

They were able to confirm this by imaging the vesicles to determine that they had the tell-tale double membrane characteristic of autophagosomes, and by testing for the presence of other compounds that serve as markers of the initiation of the cell-digesting process.

Under normal circumstances, autophagosomes contain the nutrients that are meant to be digested and recycled for other uses—but in this case, the bacteria take those nutrients to promote their own growth.

That Ats-1 could start this process on its own represents a rare power for a single protein.

"We believe this is the first bacterial protein that has been found to do this," said Rikihisa, also an investigator in Ohio State's Center for Microbial Interface Biology and Comprehensive Cancer Center. "Ats-1 initiates an early stage of the autophagosome, then picks up nutrients from the main body of the host cell and closes the layers."

Most of the action of bacterial growth takes place inside a special compartment that typically doesn't contain many nutrients. But after the Ap bacterial protein starts this process of producing autophagosomes that can encase nutrients, these bubbles fuse with the compartment, creating a steady supply of food at the site of bacterial replication and growth.

The researchers showed this by further imaging the bubbles to determine that an autophagy marker protein could be found both inside and outside of the bacterial growth compartments. They also showed that infected cells did not contain any lysosomes, which are cell parts that perform the actual digestion and degradation of foreign bodies during autophagy.

An experiment in mice deficient in the Beclin 1 protein showed that infection levels were much lower if mice had low levels of this protein—confirming its role in binding with Ats-1 and producing autophagosomes to promote infection. In cell cultures, the researchers also showed that when Ats-1 was overproduced, bacteria grew 10 times more effectively than they did in cells in which an unrelated protein was overproduced.

All of this activity allows the bacteria to remain hidden from the immune system because the induction of autophagy is considered a normal cell function and it does not produce any inflammation, which would recruit infection-fighters to the scene. Instead, the Ap bacteria set themselves up comfortably inside granulocytes and steadily grow for a few days until they rupture their host cells and generate a strong immune response—which makes an infected person sick.

In one final experiment, Rikihisa and colleagues blocked autophagosome production in Ap-infected cells using an experimental drug called 3-MA. With that process blocked, bacterial growth declined dramatically.

3-MA is toxic to humans, but its effectiveness in blocking the infectious properties of Ap in cells suggests that its structure could serve as the basis for a safe small-molecule drug, Rikihisa said.
"A similar compound could be a potential treatment to inhibit bacterial growth," she said.

Clarifying the power of Ats-1 in inducing autophagy also suggests that this protein could be an important tool in further studies of this complex cell process that remains poorly understood, she added.

**Journal Reference:**

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**Cancer Drug Shows Promise in Eradicating Latent HIV Infection ***

ScienceDaily (Nov. 29, 2012) — Breakthrough drugs have made it possible for people to live with HIV longer than ever before, but more work must be done to actually cure the disease. One of the challenges researchers face involves fully eradicating the virus when it is latent in the body. A new report appearing in the December 2012 issue of the *Journal of Leukocyte Biology* suggests that a cancer drug, called JQ1, may be useful in purging latent HIV infection by activating the virus in the presence of potent therapy—essentially a dead end for the virus.

"This drug may be useful as adjunctive therapy in efforts to purge latent HIV reservoirs to eradicate infection," said Monty A. Montano, Ph.D., principal investigator from the Section of Infectious Diseases at Boston University Medical Campus, in Boston, Mass. "This drug functions synergistically with other HIV purging agents."

To make this discovery, scientists used cell lines that contained latent HIV, as well as cells from patients who were on potent antiretroviral therapy with no detectable virus in their blood. Researchers then added JQ1 to latently infected cells, at physiologic concentrations, and observed potent reactivation of latent HIV. The researchers also observed potent suppression of inflammatory genes in genome-wide expression studies using the same cells. JQ1 reactivation of latent HIV may make it vulnerable to current therapies.

"One thing that's been made clear by the decades of HIV research is that there is no magic bullet for curing this disease," said John Wherry, Ph.D., Deputy Editor of the Journal of Leukocyte Biology. "Rather, the progress that's been made has been a series of incremental steps that often build on other previously developed therapies. The hope is that the ability of JQ1 to make latent HIV 'visible' to other HIV drugs described in this report will be another cog in the gearwheel of an HIV cure."

**Journal Reference:**

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**Sources of E. Coli Are Not Always What They Seem**

ScienceDaily (Nov. 29, 2012) — U.S. Department of Agriculture (USDA) scientists have identified sources of *Escherichia coli* bacteria that could help restore the reputation of local livestock. Studies by Agricultural Research Service (ARS) scientist Mark Ibekwe suggest that in some parts of California, pathogens in local waterways are more often carried there via runoff from urban areas, not from animal production facilities.

Even though most strains of *E. coli* are non-pathogenic, the bacterium is monitored by public health officials as an indicator of water quality. Cows are often seen as the culprits when *E. coli* is found in local lakes, rivers and other bodies of water.

Ibekwe, who works at the ARS U.S. Salinity Laboratory in Riverside, Calif., and his colleagues collected 450 water and sediment samples from 20 sites throughout California's middle Santa Ana River Watershed. The collection sites included urban areas, livestock feeding areas, parks, National Forest lands, and three wastewater treatment plants.

Then the scientists extracted *E. coli* bacteria from each sample and identified 600 different isolates of *E. coli* in their samples, many of which could be placed into six clonal populations. They found the greatest variety of different types of *E. coli* in runoff discharged from areas dominated by urban development or human activities.

Ibekwe also tested all the *E. coli* isolates for resistance to various antibiotics. He found that from 88 to 95 percent of the isolates were resistant to rifampicin, and that around 75 percent were resistant to tetracycline. Tetracycline resistance was by far the most common type of resistance observed in *E. coli* isolates collected near wastewater treatment plants.
The scientists also found that 24 percent of E. coli collected in sediment samples associated with urban runoff—a total of 144 isolates—showed resistance to as many as seven antibiotics. Results from this work were published in *PLOS ONE*.

**Journal Reference:**