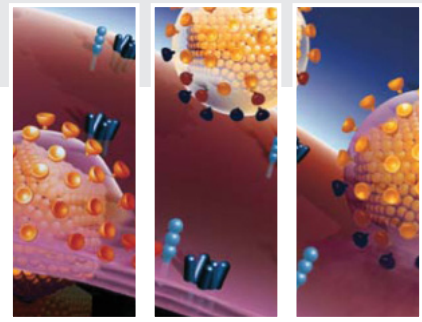


BULLETIN BOARD

Studies cast doubt on popular theory for STEP failure

Scientists investigating the failure of Merck's STEP HIV-1 vaccine trial have disproved the popular theory that pre-exposure to the adenovirus (Ad)5 virus, used as a vector for three HIV immunogens, raised levels of CD4 cells specific to Ad5, thereby creating a platform for HIV to establish infection.

The studies, conducted at the Wistar Institute Vaccine Center University of Pennsylvania (PA, USA) and the Beth Israel Deaconess Medical Center (BIDMC) in Boston (MA, USA), analyzed frozen blood samples from two different precursor trials to STEP and were published in two papers in *Nature Medicine*.

Merck halted the Phase IIb trial in 2007 after interim analysis revealed that the vaccine candidate offered no protection against HIV-1. It later emerged that trial participants with prior exposure to Ad5, the common cold virus, were more likely to be infected with HIV.

Prior exposure to the Ad5 cold virus leaves a large number of individuals with baseline neutralizing antibodies against Ad5. "This raised the possibility that these antibodies were triggering production of Ad5-specific T cells [$CD4^+$] that were susceptible to HIV-1 infection, thereby leaving study subjects at greater risk of acquiring the virus itself," explains Barouch.

"But our findings challenge this hypothesis. It does not appear that the potential enhancement of the HIV-1 infection in the STEP study was the result of these secondary, vector-specific $CD4^+$ T-cell responses."

"Moreover, subjects with baseline Ad5-specific neutralizing antibodies did not develop higher levels of Ad5-specific T-cell responses as compared with subjects without baseline Ad5-specific neutralizing antibodies."

"Our findings disprove the favored hypothesis," claims co-lead author Hildegund CJ Ertl, Director of the Wistar Institute Vaccine Center. "There was nothing to indicate that pre-existing neutralizing antibodies correlated with numbers of activated $CD4^+$ T cells to Ad5, which could have provided additional targets for HIV infection following subsequent exposure."

"Ad-specific CD4 T cells are exceptionally common in humans, regardless of the level of neutralizing antibodies to Ad5," says Michael Betts. "This is probably the major factor that disproves the main hypothesis proposed to explain the STEP trial results."

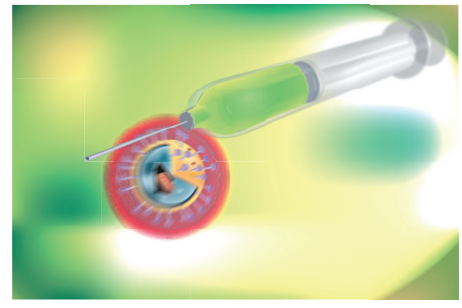
The team next questioned whether the Ad5-specific CD4 T cells functioned any differently before or after administering the Ad5 vector. They found no significant difference in activation or expansion of CD4 T-cells in either the high- or the low-Ad5 antibody groups.

"It doesn't appear that vaccination increases the pool of potentially infectable CD4 T-cells in people with pre-existing immunity to Ad5," Ertl surmises. "When you look at the data together, they suggest we must look elsewhere to explain the link between previous Ad5 immunity and increased acquisition of HIV infection."

"The two papers really biologically have shown that there's no relationship between Ad5 seropositivity and increased acquisition [of HIV]," Alan Bernstein, Executive Director of Global HIV Vaccine Enterprise told the *New Scientist*. "[This] result really rules out the possibility that it was the vaccine itself, and the fact that we used Ad5, that was somehow increasing susceptibility to acquiring [HIV] in those volunteers."

Sources: Hutnick NA, Carnathan DG, Dubey SA *et al.*: Baseline Ad5 serostatus does not predict Ad5 HIV vaccine–induced expansion of adenovirus-specific $CD4^+$ T cells. *Nat.Med.* (2009) (Epub ahead of print); O'Brien KL, Liu J, King SL *et al.*: Adenovirus-specific immunity after immunization with an Ad5 HIV-1 vaccine candidate in humans. *Nat. Med.* (2009) (Epub ahead of print); http://www.the-scientist.com/blog/display/55828/

in the news...



SIV-infected chimpanzees progress to AIDS

Researchers have identified an AIDS-like disease in SIV-infected chimpanzees living in Tanzania, overturning the prevailing idea that SIV infections are nonpathogenic.

The study, involving an international consortium led by Beatrice Hahn, University of Alabama (AL, USA) monitored and tested a group of free-ranging, but habituated, chimpanzees for any symptoms of HIV-like disease is published in *Nature*.

African primates are naturally infected with over 40 types of SIV. HIV-1 and -2 originated in chimpanzees and sooty mangabeys after jumping the species barrier sometime in the last century.

The researchers followed 96 chimpanzees living in two groups. Analyses revealed a ten- to 16-fold increase in age-corrected death hazard for SIV-infected chimpanzees compared with uninfected chimpanzees. Females were also less likely to give birth and had a higher infant mortality when they did.

Postmortem analysis of chimpanzees that died over the course of the 9-year study revealed depleted $CD4^+$ T-cell counts. There was evidence that SIVcpz is associated with progressive $CD4^+$ T-cell loss, lymphatic tissue destruction and premature death.

"When I first looked at these samples I was taken aback," recalled Karen Terio, a veterinary pathologist from the University of Illinois (IL, USA). "Slides from one of the chimps showed extreme lymphatic tissue destruction, and looked just like a sample from a patient who has died of AIDS."

The study was confined to the Gombe National Park in Tanzania, where chimpanzees have become habituated to humans since Jane Goodall began studying there nearly 50 years ago. It became possible to identify SIV-infected chimpanzees after Brandon Keele Rebecca Rudicell developed a noninvasive assay to detect SIV infection using only fecal samples at the University of Alabama.

> *"You can regard the study as one that provides a missing link in the history of the HIV pandemic ... If we identify the evolutionary adaptations, that opens up therapeutic avenues for HIV disease."*

"At this point we cannot be too precise about the magnitude of the effect, because the number of chimpanzees surveyed is still limited", says Jamie Holland Jones, an anthropologist at Stanford University (CA, USA) involved in the study, "nevertheless, the evidence is clear that infected apes have lower survival rates".

"It is a pretty momentous study," Danny Douek, chief of the human immunology section of the NIH vaccine research center (MD, USA) told the *LA Times* and was not involved in the study.

"You can regard the study as one that provides a missing link in the history of the HIV pandemic," said Douek, "If we identify the evolutionary adaptations, that opens up therapeutic avenues for HIV disease."

Another consequence of SIV-infected chimpanzees developing AIDS is that the primate does not possess inherent characteristics that confer complete protection, negating that line of investigation.

Source: http://www.uabcfar.org/docs/Dr_Hahn_findings_Nature.pdf

in brief...

Jin J, Sherer NM, Heidecker G, Derse D, Mothes W: Assembly of the murine leukemia virus is directed towards sites of cell–cell contact. *PLoS Biol.* 7(7), e1000163 (2009).
While scientists know that viruses assemble at sites of cell–cell contact, no one knew how this was achieved, until now. In a recent study, researchers used real-time imaging technology to watch how the virus gather near adjacent cells, allowing it to directly infect one cell from another. This tendency is thought to play a role in the pathogenicity of viruses such as HIV, as this method of cell-to-cell transmission keeps the virus hidden from the immune system.

The team, led by Walther Mothes of Yale University School of Medicine (CT, USA), found that the virus, through the retroviral protein Gag, was directed to the sites of cell contact by the viral glycoprotein Env, which binds to a receptor found there. This results in an approximately tenfold increase in the number of viruses assembled at these points. This novel function of Env was found to be reliant on the cytoplasmic tail of the protein, as viruses that had the tail removed did not preferentially assemble at the cell–cell contact sites.

Plantier J-C, Leoz M, Dickerson JE *et al.*: A new human immunodeficiency virus derived from gorillas. *Nature* (2009) (Epub ahead of print).
An unusual strain of HIV-1 has been identified in a 62-year-old Cameroon woman living in Paris, France. The virus resembles SIV that infects gorillas. This could be the first case of HIV-1 infection clearly linked to a nonchimpanzee lineage.

A European team, with the help of a team from The University of Manchester, identified the strain RVF168A. They propose classifying it as a group F virus, to join the established groups M, N and O of HIV-1.

The woman, the only person identified with the novel strain, moved from a semi-urban area of Cameroon to Paris in 2004. She reports no contact with gorillas or with bush-meat and the virus is capable of replicating in human cells, so it is believed that she contracted the infection from a human source. This suggests more infections will be identified.

■ About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of *HIV Therapy*. If you have newsworthy information, please contact Tony Scully, Assistant Commissioning Editor, *HIV Therapy*; Future Medicine Ltd, Unitec House, 2 Albert Place, London N3 1QB, UK; Tel.: +44 208 371 6090; Fax: +44 208 343 2313; t.scully@futuremedicine.com

Novel *in vitro* test to help predict effect of HIV microbicides on genital tract

Scientists have developed an *in vitro* test to help inform whether candidate microbicide gels against HIV are safe for human use. The test may also help explain why certain microbicides actually increased the risk of HIV infection.

The research team at Albert Einstein College of Medicine of Yeshiva University (NY, USA) have constructed a model that mimics the tissue structure of the genital tract. The model is composed of two chambers separated by a barrier of cultured epithelial cells.

If a microbicide gel inflames cells of the vaginal lining, an influx of T cells could assist HIV establishing infection and thereby increase the risk of contacting HIV. But a chemical may directly affect tissue structure. After applying different microbicides to the epithelial cells, the researchers tested the barrier's permeability, by measuring the transepithelial electrical resistance, to HIV by placing HIV in the upper chamber and CD4 cells in the lower.

"Our goal was to develop assays that are predictive of safety before proceeding to clinical trials that typically cost million of dollars, involve thousand of women , and take many years," says Betsy Herold of Albert Einstein College of Medicine, who led the team.

When a placebo gel was applied to the epithelial barrier HIV did not infect the CD4 cells in the lower chamber, "But when we applied nonoxynol-9, the virus went right through the barrier and infected the T cells", reveals Herold. This may help explain why it also actually increased the risk of HIV infection in women enrolled in Phase III clinical trials.

"Our findings strongly suggest that microbicides can increase the risk of HIV infection through a mechanism other than inflammation namely, by disrupting the protective epithelial cell barrier," suggest Harold. "If confirmed by further studies, this assay should be used early on to screen for microbicide safety before advancing a product to clinical trials involving thousands of women."

The team then employed their novel assay to test two promising microbicide, tenofovir and PRO 2000, currently in clinical efficacy trials. Neither disrupted the epithelial barrier.

Sources: Mesquita PM, Cheshenko N, Wilson SS *et al.*: Disruption of tight junctions by cellulose sulfate facilitates hiv infection: model of microbicide safety. *J. Infect. Dis.* 200, 599–608 (2009); www.aecom.yu.edu/home/news.asp?id=381

Circumcising HIV-infected males does not offer women protection

A trial investigating the efficacy of male circumcision in preventing HIV transmission to females has been halted after failing to reduce rates of HIV infection in female sexual partners.

The unblinded, randomized controlled trial has been halted early owing to its inability to demonstrate that circumcision of HIV-infected men reduced the risk of HIV transmission to female sexual partners, contrary to previous observational studies.

Three trials of male circumcision in HIV-negative men demonstrated that circumcision reduced male acquisition of HIV by up to 60%. As a result, male circumcision is now a recommended strategy for HIV prevention in men.

The trial enrolled 922 uncircumcised HIV-infected men aged between 15 and 49 years with CD4 cell counts over 350 cells or more in Uganda. In total, 474 men were randomly assigned to receive immediate circumcision and 448 participants were to be circumcised 24 months later. In this trial the organisers also enrolled HIV-uninfected female partners, with follow-up at 6, 12 and 24 months to assess HIV acquisition by male treatment assignment.

The cumulative probability of a woman being infected at 12 months was 21.7% in the intervention group, compared with 13.4% in the control group, leading the study authors to conclude that: "Circumcision of HIV-infected men did not reduce HIV transmission to female partners over 24 months".

Attributing the higher rate of infection in the intervention group to couples resuming sexual relations before the penis had fully healed, the authors stressed that "condom use after male circumcision is essential for HIV prevention."

These results have grave implication for widespread circumcision programs that are currently being rolled-our across Africa: The findings are also relevant to counseling programs, which should emphasize that sexual intercourse should not be resumed before the penis has healed.

It must be stressed that women will benefit from the implementation of widespread circumcision programs; previous studies have indicated circumcision can prevent a number of men from contracting the virus in the first instance. The authors recommend that male newborns and young boys be circumcised as soon as possible and permissible.

Source: Wawer MJ, Makumbi F, Kigozi G *et al.*: Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet* 374(9685), 229–237 (2009).