

RETROVIRUS MEETING

HIV/AIDS Researchers Reach for High-Hanging Fruit

MONTREAL, CANADA—As Ringo Starr once sang, “It don’t come easy.” That was the unofficial refrain at the HIV/AIDS meeting held here last week, the largest annual gathering for the field in North America.

The 4200 researchers who attended the 16th Conference on Retroviruses and Opportunistic Infections heard about steady progress on several fronts, but unlike in years past, there was hardly a peep about new anti-HIV drugs and no major surprises surfaced about existing treatment or prevention strategies. “There’s nothing that knocks my socks off,” said Mario Stevenson, a virologist at the University of Massachusetts, Worcester, who helped organize the meeting. “We’re in an era of just hammering away at AIDS. We’re not going to have breakthroughs and eureka

moments at every meeting.” Yet the presentations here did offer many unexpected findings on a wide range of topics, including microbicides, the search for a cure, “elite controllers,” and even chimpanzees.

The most talked about prevention study starkly illustrated that “success” now often comes with a long list of provisos. Trials of microbicide gels to protect women against HIV infection have a perfect record: Not one has worked, and some were even harmful. Now, however, a large international study of a vaginal microbicide called PRO 2000 may have finally ended that curse, although the gel’s benefits appear to be modest and require confirmation.

Epidemiologist Salim Abdool Karim of the Centre for the AIDS Programme of Research in Durban, South Africa, reported that PRO 2000 reduced the risk of HIV infection by 30% during the 3-year, \$90 million study, which involved 3000 sexually active women in four sub-Saharan African countries and the United States. Before intercourse, the women used PRO 2000, another experimental microbicide called BufferGel, an inert placebo gel, or nothing at all. The 750 women in the PRO 2000 arm of the study had 36 HIV infections, whereas the other groups had between 51 and 54 infections each.

Although this was a low level of protection and the finding did not reach statistical



Harm’s way. New evidence from chimpanzees in Gombe suggests that SIVcpz, contrary to common wisdom, can outwit their immune systems and cause AIDS.

significance, Karim emphasized that women in much of sub-Saharan Africa often do not have the option of using condoms. “In that population, 30% protection to me is a big difference,” said Karim. “Finally, there’s been a signal in the microbicide field, and that’s a thrilling event,” said epidemiologist Sten Vermund of Vanderbilt University in Nashville, Tennessee.

The study lends support to an all-but-rejected prevention approach, a microbicide gel with a so-called nonspecific mechanism. PRO 2000 has a negative charge that theoretically can bind to positively charged HIV surface proteins, blocking the virus’s ability to infect cells. Several failures of such nonspecific approaches have led many investigators to place their bets on products that incorporate anti-HIV drugs. A larger study of PRO 2000 is under way and should determine whether it works later this year, but even the cautious are hopeful. “It’s exciting to find a positive trend,” said a skeptic of nonspecific approaches, virologist Robert Grant of the University of California, San Francisco (UCSF).

For the HIV-infected, the most pressing question is whether treatments can eliminate the virus altogether—a cure. Anti-HIV drugs can powerfully suppress the virus, but ultrasensitive assays have shown that no one has eliminated it. How the residual

virus persists in blood and tissues is not clear.

One camp holds that drugs do not stop all replication, allowing the virus to constantly infect new cells and copy itself at low levels. This, in turn, replenishes a reservoir of infected, long-lived cells that otherwise would die off in a few years. If so, then intensifying treatment with more potent drug cocktails could knock out the virus entirely.

Virologist Robert Siliciano of Johns Hopkins University in Baltimore, Maryland, and colleagues tested that hypothesis by adding powerful anti-HIV drugs to the cocktails people with undetectable levels of virus were already taking. “What happens is that nothing happens,” said Siliciano. “Intensification has no effect on residual viremia.”

This finding, he says, lends credence to another theory for HIV persistence: that the infected reservoir is made up of cells that provide immunologic memory for decades and thus is stable and does not need to be replenished. If so, drugs that target viral replication can never eradicate the reservoirs, he said, and a cure will require a different strategy.

Researchers have long hoped that “elite controllers,” the small percentage of infected people in whom the virus remains undetectable for many years on the standard test *without* taking anti-HIV drugs, may have effective immune responses that hold clues for vaccine makers. Steven Deeks of UCSF, however, had dispiriting news about these lucky few.

Deeks’s studies suggest that in the majority of these controllers, the immune system works overtime to thwart the virus—with deleterious effects. These elite controllers have high levels of “activation,” an inflammatory state caused by the immune system laboring to control HIV. That activation depletes critical CD4 white blood cells, the hallmark of AIDS; it also causes systemic inflammation that contributes to atherosclerosis and other complications. Indeed, four of 58 elite controllers he studied progressed to AIDS despite having only residual viremia. “If I were an elite controller, I’d seriously think about going on treatment,” he said.

In 40% of elite controllers, another immune mechanism seems to control HIV, but Deeks says he has no idea what that is. These controllers do not have high levels of activation, nor do they have much T-cell immunity—which many believe is a key immune response to battle HIV.

Both of these findings throw a curve ball to vaccine makers. Researchers assume that even if an AIDS vaccine does not stop an infection, it will bolster immune systems so people who do become infected effectively become elite controllers. But if most elite controllers suffer from immune activation, this becomes a far-from-ideal outcome. The second group of controllers who do not have an activation problem further confound the vaccine search, as T-cell immunity is a cornerstone of most products under development. Is there another critical immune response that vaccine makers need to target?

One of the biggest surprises at the meeting came from studies of wild chimpanzees. Researchers have long assumed that SIVcpz, the chimpanzee virus that infected humans and triggered the AIDS epidemic, caused no harm to apes. But new data reveal that wild chimps infected with SIVcpz are more likely to die than are uninfected chimps. The ani-

systems had evolved to coexist with the virus. But few SIVcpz-infected chimps in the wild were identified until about a decade ago, when researchers led by Beatrice Hahn of the University of Alabama, Birmingham, developed a way to routinely test fecal samples for evidence of the virus. Although SIVcpz has not been found in several chimp communities studied, some have a prevalence as high as 35%.

Rebecca Rudicell, a graduate student in Hahn's lab, reported that she and her colleagues analyzed 1099 fecal samples collected between 2000 and 2008 from chimpanzees living in Gombe Stream National Park in Tanzania. They found evidence of SIVcpz infection in 18 chimps. Seven of the 18 infected chimps died during the study period, compared with 10 of 76 uninfected animals, said Rudicell. When they corrected for age and other variables, the scientists found that the SIVcpz-infected chimps had a 15-fold higher risk of death than did virus-free apes, meaning that SIVcpz poses nearly as great a risk as HIV-1 does to humans. Studies of lymph nodes from two of the infected chimps that died also showed the type of immunologic destruction seen in HIV-infected humans. And these chimps had low

levels of CD4 cells, the lymphocytes that are the main targets of SIVcpz and HIV-1. "We were shocked at the initial discovery of SIVcpz in the Gombe chimps and even more dismayed when we established that it seems to be pathogenic," said behavioral ecologist Anne Pusey, who runs the Jane Goodall Institute's Center for Primate Studies at the University of Minnesota, Twin Cities, and collaborates with Hahn. "It must be the case that some of the [chimp] mortality over the last decades has been due to SIV." During their study period, the prevalence ranged from 9% to 18%, which mirrors the devastating levels of infections seen in human populations in the hardest

hit countries in sub-Saharan Africa.

The finding raises provocative questions about the relationship between HIV-1 and SIVcpz. For instance, why does SIVcpz harm chimp immune systems when HIV-1 doesn't? The work might offer clues to vaccine makers, too, about which immune responses to target. Also unknown is whether SIVcpz has contributed to the alarming chimp decline seen elsewhere. But once again, the answers to those questions surely won't come easy. —**JON COHEN**

ScienceInsider

From the Science Policy Blog



Lifestyles of the rich and famous. That's one way to describe the world of science this week. Here are some highlights from our science policy blog, *ScienceInsider*.

First the **rich**. Science agencies continued to rack up billions, as Congress finally completed work last week on a \$787 billion economic stimulus package. The biggest winner is the National Institutes of Health, which would receive \$10 billion for research and facilities. Also seeing green is the Advanced Research Projects Agency for Energy, established by Congress 2 years ago to inspire risky energy and climate-related research. The concept hadn't gotten a dime in the regular appropriations, but lawmakers threw \$400 million at it as part of the stimulus.

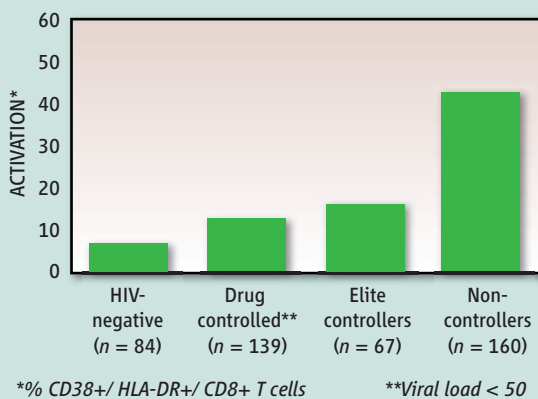
Now for the **famous**, and it doesn't get any more famous than Tom Hanks. This week, the movie star stopped by CERN near Geneva, Switzerland, to chat about *Illuminati* and antimatter. So what does he think of the world's largest particle physics laboratory? "I love seeing science fiction become science fact," he told one of our reporters on the scene. Speaking of CERN, its Large Hadron Collider should be back in business by late September.

In **Washington**, John Holdren and Jane Lubchenco sailed through a joint Senate confirmation hearing, while the House of Representatives passed legislation to overhaul environmental and safety research related to nanotechnology. If the Senate follows suit, the new law will set up a nano czar in the White House and require a research plan.

Finally, what do you get when you cross a vacuum cleaner with a tree? A potential **geoengineering** solution called air capture, which aims to lower atmospheric CO₂ levels by literally sucking the greenhouse gas out of the sky. We smell a sci-fi movie. Someone get Tom Hanks.

For the full postings and more, go to blogs.sciencemag.org/scienceinsider.

HIV Replication Drives Immune Activation



Control issues. Untreated HIV-infected "elites" have higher levels of immune activation than do people who suppress their virus with drugs.

mals also show AIDS-like damage to their immune systems. The finding raises the possibility that some chimp populations are suffering from AIDS epidemics.

Evidence suggests that SIVcpz, discovered in 1989, is most closely related to HIV-1 and predates it. Captive chimps experimentally infected with HIV-1 typically suffer no harm, which led several researchers to propose that chimps had lived with SIVcpz for centuries and that their immune