

RETROVIRUS MEETING

Novel Attacks on HIV Move Closer to Reality

At a recent conference, AIDS researchers reported new insights into the epidemic's origins and progress on treatment and prevention

DENVER, COLORADO—Neither the hunt for an AIDS vaccine nor the search for a cure has made much progress lately, but at the 13th Conference on Retroviruses and Opportunistic Infections held here last week, researchers reported several advances that may lead to novel ways to treat and prevent HIV infection, as well as to a clearer understanding of the epidemic's origins.

Perhaps most encouraging, said one of the meeting organizers, Constance Benson of the University of California, San Diego, a powerful new drug that cripples HIV's ability to weave itself into human chromosomes has made an important leap forward in human trials. The drug, made by Merck and dubbed MK-0518, inhibits the integrase enzyme, which the virus requires to copy itself. The antiretroviral drugs now on the market target different parts of HIV's life cycle.

Beatriz Grinsztejn of the Oswaldo Cruz Foundation in Rio de Janeiro, Brazil, described

an antiretroviral. If the drug works in larger trials and serious toxicities do not surface, said Benson, "it will change the paradigm of treatment." Merck is launching two studies in several countries to assess MK-0518's safety and efficacy in large groups of people with drug-resistant infections and hopes to seek U.S. approval next year.

Prophylactic progress

A monkey experiment of two anti-HIV drugs already on the market, tenofovir and FTC, shed new light on a promising prevention strategy. Researchers are staging six trials around the world in HIV-*un*infected but high-risk people to see whether tenofovir alone can work as so-called pre-exposure prophylaxis (PrEP), thwarting the virus if a person is exposed. Early studies in monkeys with tenofovir PrEP demonstrated its potential, although last year, researchers from the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, reported that the protection didn't seem robust. Tenofovir PrEP solidly thwarted an intentional attempt to infect the animals once, but by the 15th "challenge" with the AIDS virus, no animal remained protected.

In a new study of the same design, CDC's Walid Heneine and co-workers added FTC to tenofovir (a combination drug sold commercially as Truvada) and found that all six monkeys remained protected

after 14 challenges. "I think it's fantastic," said Myron Cohen of the University of North Carolina, Chapel Hill. "It's an extremely compelling piece of work that raises the ante of what we should test."

HIV's origins

Two groups studying wild chimpanzees in Cameroon reported progress in deciphering HIV's origins. These teams previously had discovered persuasive evidence that chimps harbor a simian immunodeficiency virus called SIVcpz that became HIV-1—the predominant cause of



Dirty work. To find new isolates of the virus that evolved into HIV-1, researchers in Cameroon collected more than 1000 samples of ape feces.

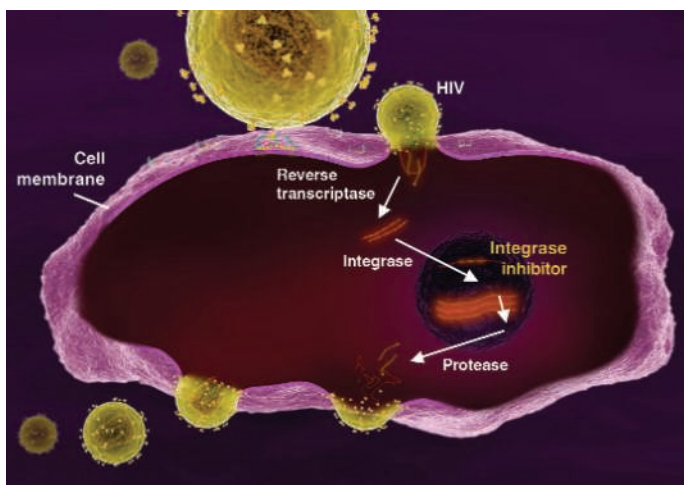
AIDS in humans—but they had found precious few infected animals with which to make the case. By analyzing 1300 fecal samples from wild apes, the groups found SIVcpz in several geographic areas and then genetically characterized dozens of new isolates. "They're closing in on some very hot stuff," said James Hoxie, who studies HIV and SIV at the University of Pennsylvania. "It's compelling genetic evidence."

The new work found more than 30 strains of SIVcpz, tripling the number previously discovered. The researchers took advantage of the fact that chimps cannot swim, which means that rivers naturally separate different communities and block the spread of viruses. For the first time, they found chimp communities in which SIVcpz infection was widespread—in one, up to 35% of the individual animals analyzed had the virus in their feces. "Our eyeballs popped out of our heads," said Brandon Keele, who works with Beatrice Hahn at UAB. In a separate presentation, Fran Van Heuverswyn, part of a team headed by Martine Peeters of the Institut de Recherche pour le Développement in Montpellier, France, described how two of the isolates more closely matched HIV-1 causing the human epidemic than any found in the past.

Building on the new data, Paul Sharp, who studies molecular evolution of pathogens at Nottingham University in the U.K., went a step further back in time to explain the origin of SIVcpz. Researchers have discovered different SIVs in more than 30 species of monkeys. Sharp's new analysis suggests that the SIVcpz closest to HIV-1 is a combination of SIVs isolated from red cap mangabeys and monkeys from the *Cercopithecus* genus.

Filling in the final piece of the origin puzzle, Sharp said the virus must have reached a major city to start the AIDS epidemic. He posited that a person became infected in rural Cameroon and then traveled by river to Kinshasa, Democratic Republic of Congo. Kinshasa has the greatest genetic diversity of HIV-1, suggesting that the virus has been there longer than anywhere else. It also was home to the first known HIV-infected person, a Bantu man who had his blood sampled in 1959 for a malaria study.

—JON COHEN



New target. An integrase inhibitor may soon join the arsenal of anti-HIV drugs that attack reverse transcriptase, protease, and viral entry.

a multisite, placebo-controlled clinical trial of MK-0518 that involved 167 people infected with multidrug-resistant HIV. MK-0518 lowered the level of HIV to below 400 copies per milliliter—a 99% drop—in 80% of the treated participants. "That's a tough population, and to get 80% [of patients] below 400 copies is about as good as it gets," said Michael Saag, who heads the AIDS research center at the University of Alabama, Birmingham (UAB).

A smaller, shorter study reported last fall revealed that the drug was also safe and potent in HIV-infected people who had never taken