

INFECTIOUS DISEASES

Doubts dispelled about HIV prevention

New studies show remarkable efficacy and versatility of drugs for uninfected

By **Jon Cohen**, in Seattle, Washington

It was great news for HIV prevention, and few seemed to hear it. Five years ago, researchers showed that people likely to be exposed to HIV can cut their risk of infection with a simple pill, but the strategy has been slow to catch on. At the Conference on Retroviruses and Opportunistic Infections (CROI) here last week, a bevy of new studies quelled most remaining doubts about the real-world effectiveness of what's known as pre-exposure prophylaxis (PrEP), showed practical ways to use it, and suggested that it could help change the trajectory of the epidemic.

"This meeting is a watershed event for PrEP," said Robert Grant, a virologist at the University of California, San Francisco (UCSF), one of the pioneers of this approach. Others likened the meeting to the 1996 AIDS conference in Vancouver, which broadcast to the world that potent cocktails of antiretroviral (ARV) drugs could effectively treat the infection.

Grant led a pivotal study of PrEP that showed in 2010 how the ARV Truvada cut the rate of new infections in men who have sex with men (MSM) and transgender women by 92%—if they took the pill daily. The problem was that about half the people in the study didn't, which left the overall efficacy at a modest 44%. Later, a large study in heterosexual "discordant" couples, in which only one partner was infected, found that adherence was much better, yielding 75% protection.

But, despite approval by the U.S. Food and Drug Administration, PrEP has never gained much traction. Health workers have hesitated to prescribe it because of worries that PrEP would lead men to forgo condoms—so-called behavioral disinhibition—negating much of the benefit. Some at-risk people have not used PrEP because they fear it will brand them as promiscuous or reckless. Young, single women appear especially reluctant to use the drug. "Adherence

[is] the Achilles' heel of PrEP," said Jean-Michel Molina of Paris Diderot University.

In a study called IPERGAY, Molina and his colleagues investigated whether PrEP might work better if people did not have to take pills every day. They tested a more convenient "on-demand" regimen in 414 HIV-negative, high-risk MSM in France and Canada. The men were instructed to take pills—without knowing whether they contained Truvada or a placebo—before and after having sex. As Molina ex-

545 MSM in the United Kingdom, gave the conventional regimen of PrEP to half the participants and compared their behavior and HIV infection rates with a control group that started PrEP a year later. This design differed from the initial studies in MSM in two key ways: No one received a placebo, and participants knew that, if used, the pills offered strong protection.

PROUD was stopped early after 19 people in the deferred group became infected compared with three in the immediately

treated group—again, 86% efficacy. Other sexually transmitted infections or reported sexual behavior were no different in the treated and control groups. "Our concerns that PrEP would be less effective in the real world were unfounded," said PROUD's leader, Sheena McCormack of University College London.

A third, ongoing study led by Jared Baeten of the University of Washington, Seattle, identified a way to boost the effectiveness of PrEP in discordant couples. If an infected partner takes ARVs and fully suppresses the virus, there is little risk of transmission. But some infected people opt not to take the drugs or do not have access to them. And even in those who do start treatment, it can take several months for the drugs to reach full power, leaving a window for transmission. Baeten and colleagues explored ways to deal with those scenarios.

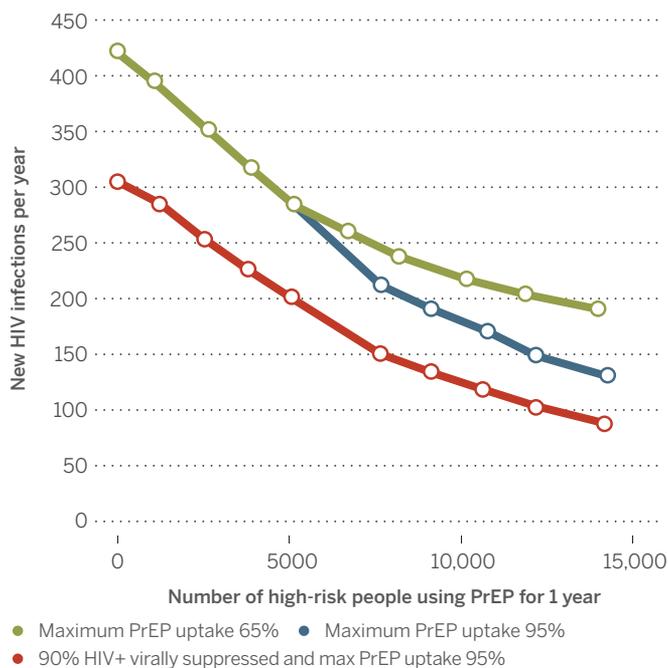
In 1013 discordant couples in Kenya and Uganda, the researchers are offering PrEP to all uninfected people to protect them for the first 6 months after their

partners start ARVs. In couples where the infected partner does not start treatment, the PrEP "bridge" is extended for as long as necessary. To date, only two people have become infected in the study, compared with 40 predicted by modeling, and neither had Truvada in their blood when transmission occurred. Baeten said that using PrEP as a bridge "is not only feasible in this higher risk population, but highly effective."

The potential payoff of widespread PrEP could be huge, UCSF's Grant showed in a

The pills that could blunt an epidemic

A model shows that widespread use of pre-exposure prophylaxis, especially when combined with increased treatment of HIV-infected people, could change the course of San Francisco's epidemic.



plained, 14 people became infected in the placebo group versus two in the treated arm—both of whom had stopped taking the drug months before their infections occurred—amounting to an 86% drop in infections. "On-demand PrEP could be a game changer in PrEP use," Molina said.

A second study found that adherence might not be as big a problem in the real world as it was in the initial studies and that behavioral disinhibition did not occur. The PROUD trial, conducted in

modeling study of the San Francisco epidemic, in which only 31% of people at high risk of infection used PrEP at some point last year. If 65% of these people used PrEP for 12 months, the number of annual new infections would be halved. That drop

could double again by aggressive use of both PrEP and treatment (see graphic). “We’re at a tipping point where PrEP was a proven concept of unknown applicability,” Grant said, “and what’s most exciting is we can now see that is feasible.” ■

Drug flushes out hidden AIDS virus

By **Jon Cohen**, in Seattle, Washington

HIV/AIDS researchers call it “shock and kill”—a way to obliterate the final reservoir of latent virus that stands between an infected person and a cure. Last week at a major HIV/AIDS conference here (see main story, p. 1055), a team reported new results from a monkey study that move a few steps toward that grand but elusive goal.

Strong cocktails of antiretroviral (ARV) drugs can knock down blood levels of HIV to undetectable on standard tests, but they have not cured anyone. That’s because small “reservoirs” of long-lived cells have viral DNA sleeping in their chromosomes, where it is impervious to drugs and invisible to the immune system. So cure researchers have hunted for ways to shock these cells into producing the virus, causing them to self-destruct or be killed by the immune system.

Most cure strategies have focused on the first step: waking up the virus. But virologist James Whitney of the Beth Israel Deaconess Medical Center in Boston described a drug that appears to deliver a one-two punch: It both wakes up the virus sleeping in immune cells and then, as an added bonus, revs up the immune attack against the infected cells. “It’s a magic combination effect,” says Steven Deeks, an HIV cure researcher at the University of California, San Francisco.

Gilead Sciences of Foster City,

California, is testing the drug, known as GS-9620, in people who have hepatitis B. GS-9620 works by binding to immune cell surfaces through what is known as toll-like receptor 7 (TLR7), triggering a response that includes inducing CD4 white blood cells to make copies of themselves. These are the same white blood cells that HIV favors. Because HIV-infected CD4s produce the virus when they replicate, a team at Gilead led by Romas Geleziunas wondered whether their TLR7 drug might help eliminate HIV reservoirs.

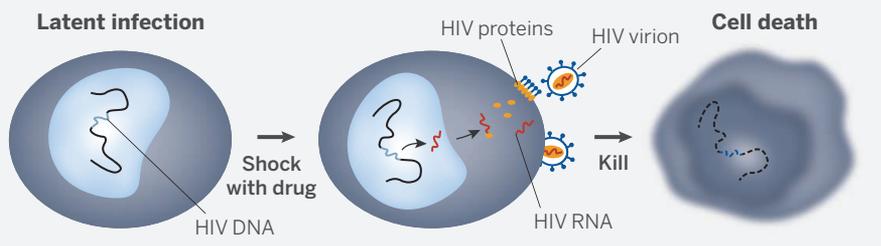
The researchers infected 10 rhesus macaques with SIV, a simian AIDS virus, and treated them with ARVs to suppress the virus to undetectable levels. Then they gave four of the animals repeated injections with an analog of GS-9620. Blood levels of SIV rose to high levels in the four treated animals, indicating that the drug had prodded reservoirs to produce virus. Other attempts to shock cells harboring latent HIV have led only to tiny blips of virus. “You don’t need binoculars to see these blips,” Geleziunas said.

The experiment did not cure the monkeys of SIV. But later analysis showed that after the shock with the drug, SIV DNA levels dropped in the blood, lymph nodes, and colons of three of four animals. That suggested the reservoir had shrunk, although the precise mechanism of cell killing is unclear.

Geleziunas says small studies of GS-9620 in HIV-infected people are about to begin. ■

Draining the reservoir

A drug that targets the TLR7 receptor shocked cells with latent HIV infections into producing the virus, setting them up for the kill.



PALEOANTHROPOLOGY

Deep roots for the genus *Homo*

Fossil jawbone pushes back origins of our genus by 400,000 years

By **Ann Gibbons**

On a hot January morning 2 years ago, Chalachew Seyoum was searching for fossils at a desolate site in Ethiopia called Ledi-Geraru, where no human ancestor had turned up in a decade of searching. But Seyoum, an Ethiopian graduate student at Arizona State University (ASU), Tempe, was upbeat after a week off. “I had a lot of energy and fresh eyes,” he says. “I was running here and there. I went up a little plateau and over the top when I spotted this specimen popping right out.”

He sat down and closed his eyes. When he opened them, he could more clearly see the gray fossil poking out of the bleached sand and mudstone, and he realized that he had found the jawbone of a hominin—a member of the human family. He called out for the ASU expedition leader: “Kaye Reeceed!” Reed scrambled up the steep slope on her hands and knees, saw the fossil, and yelled “Woo-hoo!”

Their excitement was justified. In two papers online this week in *Science* (<http://scim.ag/BVillmoare>; <http://scim.ag/ENDiMaggio>), the ASU team and co-authors introduce the partial lower jaw as the oldest known member of the genus *Homo*. Radiometrically dated to almost 2.8 million years ago, the jaw is a window on the mysterious time when our genus emerged. With both primitive and more modern traits, it is a bridge between our genus and its ancestors and points to when and where that evolutionary transition took place. As a transitional form “it fits the bill perfectly,” says paleontologist Fred Spoor of University College London.

Together with a reassessment of known fossils, published in *Nature* this week by Spoor and colleagues, the find is stimulating new efforts to sort out the mixed bag of early *Homo* remains and to work out which forms emerged first. “This causes us to rethink early *Homo*,” says paleoanthro-