INFECTIOUS DISEASE

HIV Prevention and Cure Insights Come From Failure and Success

SEATTLE, WASHINGTON—A dramatic string of successes has buoyed the HIV prevention field over the past 2 years, but a troubling question has lingered: Why did a seemingly simple strategy work in some groups but not others? Last's week meeting* here brought a sobering answer that may guide future prevention efforts. Research on ways to cure HIV infections also received more attention than ever.

One of the most discussed prevention interventions at the meeting, pre-exposure prophylaxis (PrEP), gives anti-HIV drugs to uninfected people. Since July 2010, large clinical trials of PrEP have shown that it works in heterosexual couples with an HIV-infected partner, in men who have sex with men (MSM), and in some single women but not others. At the meeting, an analysis of FEM-PrEP, one of two studies that failed in single women, offered a clear explanation for its disappointing results. (Researchers have not finished assessing the second failure.)

FEM-PrEP enrolled more than 2000 women in South Africa, Kenya, and Tanzania, assigning equal numbers to take either an anti-HIV pill (a combination of tenofovir and FTC) or a placebo each day. Of the 68 women who became infected after the trial started in July 2009, 33 received the drugs, leading researchers to prematurely end the study in April 2011.

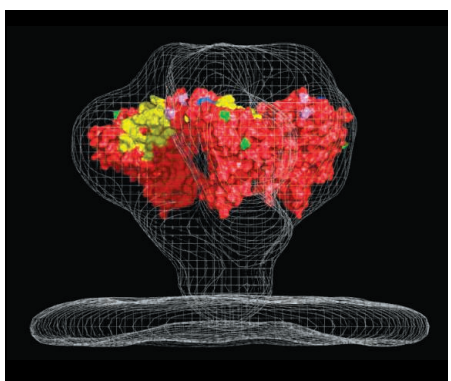
Poor adherence to drug regimens often undermines trials, but women reported taking their pills 95% of the time. In an attempt to verify this, researchers required women to return unused pills before they received monthly refills; counts suggested they had taken more than 85% of the drugs (see table). Drug concentrations in the women's blood, however, "told a very different story, despite [our] intense effort to encourage adherence in the trial," said the study's principal investigator, Lut Van Damme of FHI 360, a nonprofit organization in Durham, North Carolina.

The researchers analyzed tenofovir levels in blood samples of treated women taken shortly before and after they became infected. In sharp contrast to the pill counts, less than 26% of these women had a high enough drug concentration to stop HIV. "We do not know at this moment what exactly they were doing with those pills," Van Damme said.

*19th Conference on Retroviruses and Opportunistic Infections (CROI), 5–8 March.

The upside is that PrEP in women likely works if they take the drugs. "The data really line up," said Kenneth Mayer of Brown University, who helped prove PrEP prevents HIV infection in MSM. As a potential solution to the adherence problem, researchers are developing long-lasting drug formulations that require, say, weekly dosing.

Several conference sessions featured studies that aim to cure HIV—once a far-fetched idea (*Science*, 13 May 2011, p. 784). "It's a real mind change," said Christine Rouzioux, a virologist at Necker Hospital in Paris, who headed one of the sessions. "I fought for years to say the main problem in HIV is the reservoir."



Drug Levels in Blood Explain PrEP Failure Despite Supposed Adherence

	Drug	Placebo
Reported Usually/always took study pill	95%	95%
Reported Easy/very easy to take pills	97%	96%
Measured Pills taken (based on number returned)	86%	89%
Measured Effective drug levels in blood near time of infection	<26%	NA

Mystery solved. FEM-PrEP didn't prevent infections with HIV (its surface protein modeled *above*) because women didn't take the drugs.

A reservoir of "resting" cells in every HIV-infected person harbors the virus in a dormant state. These resting cells have long lives and fly under the immune system's radar as long as HIV's genes remain hidden inside chromosomes. Even when anti-HIV drugs drive the virus down to undetectable levels on standard tests, the resting cells maintain infections. To cure a person, researchers hope to drain reservoirs by waking up resting cells and compelling them to produce HIV, which theoretically will lead the virus to burst cells apart or target them for immune attack.

Two talks at the meeting gave tantalizing hints that drugs can potentially reduce reservoirs. David Margolis of the University of North Carolina, Chapel Hill, gave six HIV-infected people with undetectable levels of virus a marketed cancer drug made by Merck, SAHA, which targets molecules inside of chromosomes that prevent cells from expressing the virus. After one dose of SAHA, all six patients had significant increases in levels of HIV RNA inside of their resting cells, an indicator that latent virus had awoken. Similarly, a team led by Luis Montaner of the Wistar Institute in Philadelphia, Pennsylvania, found that in nine HIV-infected people who received injections with an immune-stimulating drug, pegylated interferon-alpha-2a, reservoirs of HIV-infected cells appeared to have shrunk. "It's very interesting and hypothesis-generating," said Daria Hazuda, a drug developer at Merck Research Laboratories in West Point, Pennsylvania, who collaborates with Margolis.

Yet prodding infected resting cells to produce HIV may not, by itself, reduce reservoirs. Liang Shan, who works in Robert Siliciano's lab at Johns Hopkins University in Baltimore, Maryland, reported dogma-challenging results from a test-tube study with SAHA. As Margolis did in patients, Shan activated HIV in resting cells with SAHA, but in the lab dishes, the virus did not, as expected, burst the cells apart. Adding immune cells from patients on effective anti-HIV treatment, who have weak responses against the virus because they rarely see it, also did not kill the resting cells. "We have to accept that after virus reactivation, the cells which remain at the resting state will probably not be eliminated," Shan said.

Shan suggested that cure strategies must boost the immune response against HIV before activating the latent virus. Sharon Lewin, a virologist at Monash University in Melbourne, Australia, who is studying SAHA in HIV-infected people, said it was a "really beautiful talk and a lovely model." Others were more circumspect, but Shan's findings reminded those seeking an HIV cure of a lesson learned the hard way by many investigators who were surprised by the FEM-PrEP failure: Assume nothing.

–JON COHEN

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