Long-acting, injectable drug could strengthen efforts to prevent, treat HIV
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Scientists have developed an injectable drug that blocks HIV from entering cells. They say the new drug potentially offers long-lasting protection from the infection with fewer side effects. The drug, which was tested in non-human primates, could eventually replace or supplement components of combination drug "cocktail" therapies currently used to prevent or treat the virus.

"This is an exciting new HIV therapeutic option for both prevention and treatment, with a unique mechanism of action compared to other approved drugs," says Michael S. Kay, M.D. Ph.D., a senior author of the study and a U of U Health professor of biochemistry. "It has great potential to help patients who suffer from drug resistance as well as those who would benefit from a longer-acting, injectable anti-HIV drug cocktail."

The study appears in Proceedings of the National Academy of Sciences (PNAS).

In 2019, about 1.7 million people worldwide were newly infected with HIV, according to the World Health Organization. More than 38 million people are currently living with the infection. Combination antiretroviral therapy (cART), the so-called "drug cocktail," has dramatically improved survival and quality of life for such patients, but it is also costly, often has serious side effects, and requires patients to take pills daily. In addition, because HIV frequently mutates, drug resistance is a constant challenge, Kay says, so researchers are always seeking new drugs with novel mechanisms of action to produce more robust combination therapies.

In this new study, the researchers tested a unique drug called CPT31, based on a D-peptide that targets a critical pocket on HIV's fusion machinery that rarely mutates. D-peptides are mirror images of naturally occurring peptides. To imagine it, think of right and left hands. The building blocks and overall structure of natural peptides are analogous to our left hand versus our right hand for D-peptides.

Because of that, CPT31 and other D-peptides are not degraded in the body. Therefore, they last much longer than natural peptides, making them especially suitable for a long-acting injectable formulation.

"In addition to their durability in the body, D-peptides are largely ignored by the immune system, preventing immune reactions that are a side effect often seen with traditional peptide and protein drugs," says Brett Welch, a co-author of the study and senior director of technology and strategy at Navigen, Inc.

University of Utah Health scientists led the study in collaboration with researchers from the National Institute of Allergy and Infectious Diseases (NIAID), Beth Israel Deaconess Medical Center in Boston, and Navigen, Inc.
Navigen, Inc., the Salt Lake City company that co-developed CPT31 and is managing clinical trials, "As a D-peptide, our hope is that CPT31 will provide extended viral suppression with a lower dose and reduced side effects."

To see if CPT31 could prevent HIV infection, Kay and colleagues first injected the drug into healthy macaque monkeys starting several days prior to exposure to a hybrid simian-human form of HIV called SHIV. The monkeys were completely protected from this very high SHIV exposure, much higher than what humans typically encounter, and never developed signs of infection. Subsequently, the scientists identified the minimum dose of CPT31 needed to confer complete protection, information that will help inform clinical trials.

"We think this drug could be used by itself to prevent HIV infection because initial HIV exposure typically involves a relatively small amount of virus," Kay says. "This study showed that the vast majority of circulating HIV strains from around the world are potently blocked by CPT31."

But what about later stages of the disease when there are billions of copies of the virus circulating in the body?

To find out, the researchers gave CPT31 to monkeys with untreated SHIV infections and high viral loads. Over the course of 30 days, the drug significantly lowered the presence of SHIV in their bloodstreams. However, virus levels rebound in two to three weeks due to drug resistance, as typically observed when treating established infections with a single drug.

Finally, the researchers tested the drug's ability to maintain viral suppression after a cART drug cocktail is discontinued in macaques. cART reduces SHIV to an undetectable level, but the virus rapidly rebounds after discontinuing therapy (as also seen in humans). In this study, CPT31 by itself effectively kept the virus at an undetectable level for months (until drug administration was discontinued).

"Such a simplified 'maintenance therapy' could present patients with a new option for viral control that is more cost-effective, convenient to take, and has fewer side effects," Kay says.

In parallel with clinical trials, Navigen is developing a long-acting injectable formulation of CPT31 with the goal of only requiring injection of the drug once every three months.

"Long-acting injectable formulations appear to be greatly preferred by both patients and physicians compared to current daily drug regimens that can be challenging to maintain," Welch says. "Additionally, the steady therapeutic drug levels provided by such a formulation would reduce the risk of drug resistance caused by missed daily pills, as well as reduce side effects."

Upcoming human trials, scheduled for later this year, will help determine whether CPT31 is safe and effective in humans. Kay says that the full course of human clinical trials and subsequent FDA approval could take several years.


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