New lead against HIV could finally hobble the virus's edge

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Credit: AI-generated image (disclaimer)

Since HIV emerged in the '80s, drug "cocktails" transformed the deadly disease into a manageable one. But the virus is adept at developing resistance to drugs, and treatment regimens require tweaking that can be costly. Now scientists at the 249th National Meeting & Exposition of the American Chemical Society (ACS) are announcing new progress toward

affordable drugs that could potentially thwart the virus's ability to resist them.

"This disease has gone on for over three decades," says Dennis Liotta, Ph.D. "We've got to try to find new solutions. Even with the 30 approved drugs that we have, and even when you completely suppress viral replication, we still see disease progression."

So Liotta's team at Emory University decided to tackle a seemingly intractable problem that had been plaguing efforts to defeat the virus.

To replicate, Liotta explains, HIV fuses with human immune cells by interacting with key proteins. Its genetic contents subsequently spill inside the immune cells, and the viral proteins then hijack the cellular machinery to make copies of themselves.

One drug company (Pfizer) has developed a compound that blocks HIV's interaction with one of those proteins, a co-receptor called CCR5. But the virus can also use a second co-receptor, CXCR4, to enter cells. If a drug targets just CCR5, a more virulent strain that favors CXCR4 could emerge over time, says Liotta.

In theory, drugs targeting CXCR4 would be an effective addition to the arsenal against HIV. But interfering with that protein, which regulates several of the body's inflammatory responses, could lead to serious side effects.

"With a chronic infection like HIV, it's very challenging to take a drug every day of your life if you have significant side effects," Liotta says. "This is a very high bar. No drug that functions as a CXCR4 antagonist for HIV has gotten over that bar."

Liotta's team decided to search for compounds that might be able to bind

both CCR5 and CXCR4 at the same time, while avoiding serious side effects.

"Essentially, we took a step back and said instead of creating yet another cocktail of multiple drugs to stop the different mechanisms of HIV, we thought we could design one that hit multiple targets at once," says Anthony Prosser, a graduate student in Liotta's lab. If a new drug could block HIV entry by interfering with CCR5 and CXCR4, it could be paired with a traditional cocktail targeting other stages of the virus lifecycle for an even more robust treatment.

Prosser came up with a simple, inexpensive method to synthesize compounds that likely would bind both co-receptors. Lab tests identified the most effective ones, and the group's partners at pharmaceutical company Bristol-Myers Squibb found that the compounds also blocked HIV reverse transcriptase, an enzyme that's key to the virus's ability to copy itself.

"The agents were active against CCR5, CXCR4 and HIV reverse transcriptase," Liotta says. "That was unprecedented. Also, they don't perturb any of the CXCR4 signaling pathways that lead to inflammation."

An additional benefit of this approach is that the compounds target proteins on human cells. Most HIV drugs target viral proteins, but because they often mutate when exposed to antiretroviral agents, resistance can develop quickly. When that happens, patients have to switch to a new drug combination that can be less effective than the previous treatment. Human proteins rarely mutate to a significant extent, so HIV will be far less likely get around drug combination therapies that include a CXCR4/CCR5 inhibitor, Liotta explains. Since these agents are inexpensive to prepare, they could potentially keep treatment affordable for millions, particularly in the developing world.

Now the lab is working to further control the activity of these compounds, boost their potency and minimize their potential toxicity.

"We've got a long way to go, but this is a very exciting finding," Liotta says.

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