Medical Xpress

Study identifies mechanism for drug target to help block HIV's ability to spread

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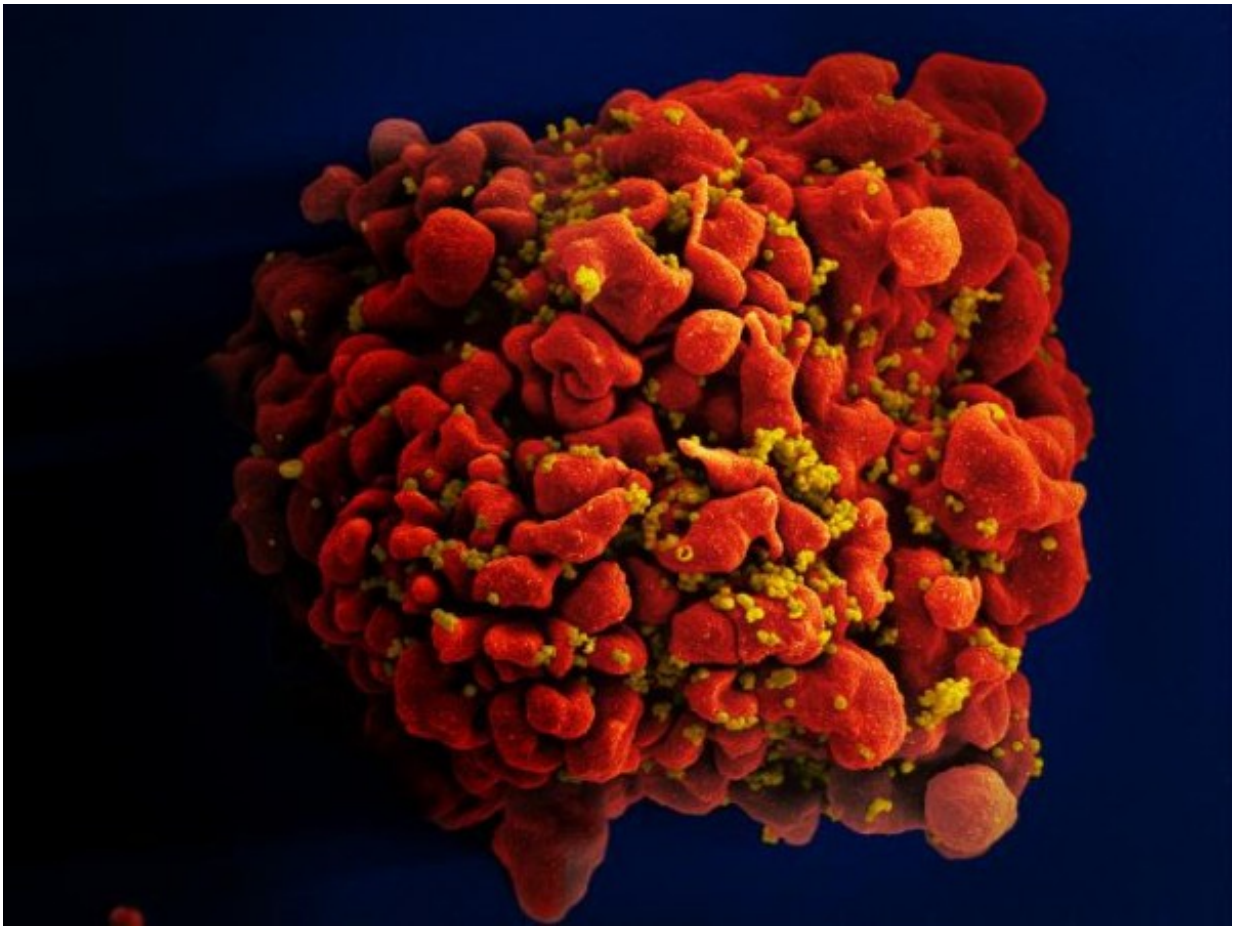

University of Minnesota researchers have identified the mechanism of a

potential HIV drug target, which could be a more cost-effective option than currently used HIV drugs.

The study expanded upon previous UMN research, which identified that the nucleoside 5-azacytidine (5-aza-C) blocked HIV's ability to spread. 5-aza-C triggers lethal mutagenesis, a process in which HIV mutations speed up to a point that the HIV essentially wears itself out.

A collaborative team of researchers at the University of Minnesota and Emory University found that 5-aza-C blocks HIV's ability to spread by first converting to a DNA form (5-aza-deoxyC). The DNA conversion allows 5-aza-C to infiltrate HIV when the virus turns RNA into DNA, and therefore stops the virus from replicating.

The majority of HIV medications currently on the market are DNA-based, but RNA-based drugs like 5-aza-C have a manufacturing advantage because they are more affordable to produce.

The study was posted online and will appear in print in the American Society for Microbiology's journal *Antimicrobial Agents and Chemotherapy* in April.

"We now understand the mechanism for how 5-aza-C blocks HIV's infectivity through hypermutation. This information may aid in developing cheaper HIV drugs," said lead-author Louis Mansky, Ph.D., Director of the Institute for Molecular Virology and professor in the University of Minnesota School of Dentistry. Mansky is also a Masonic Cancer Center member.

This also helps explain why 5-aza-C is able to block HIV infectivity, despite its RNA-origin. 5-aza-C acts similarly to its DNA-based counterpart 5-aza-deoxyC, but is not nearly as effective. However, it can be mass-produced more cheaply.

"More than half of the world's HIV population is concentrated in sub-Saharan Africa where there is very limited access to HIV drugs and treatment. Our study could lead to developing more cost-effective medication, which in turn could lead to new and more economical treatments for poorer, developing countries," Mansky said.

5-aza-C has been approved by the FDA for clinical use in treating myelodysplastic syndrome, but it's only available as an IV-based medication. The study's findings encourage efforts to explore ways to produce 5-aza-C in capsule form.

"While it's not as effective as its DNA-based form, we can use what we know to try mimicking 5-aza-C to discover new compounds that could be more effective, while still being more affordable to produce," Mansky said.

It's another step towards ultimately finding a cure for HIV, Mansky says.

In addition to being more cost-effective HIV drugs, these RNA-based drugs could have potential use in the treatment of a wide variety of emerging viral infections, including Zika virus, Ebola virus, MERS virus and influenza virus.

More information: Jonathan M.O. Rawson et al. 5-azacytidine enhances the mutagenesis of HIV-1 by reduction to 5-aza-2'-deoxycytidine, *Antimicrobial Agents and Chemotherapy* (2016). DOI: 10.1128/AAC.03084-15

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