# HIV drug stops Zika infection, strategy could halt infections caused by related viruses

October 30 2019

Credit: Temple University

Like an adjustable wrench that becomes the "go-to" tool because it is effective and can be used for a variety of purposes, an existing drug that can be adapted to halt the replication of different viruses would greatly expedite the treatment of different infectious diseases. Such a strategy would prevent thousands of deaths each year from diseases like dengue and Ebola, but whether it can be done has been unclear. Now, in new work, researchers at the Lewis Katz School of Medicine at Temple University (LKSOM) show that repurposing an existing drug to treat

viral diseases is in fact possible—potentially bypassing the decades needed to develop such a broad-spectrum drug from scratch.

In a new study published in the journal *Molecular Therapy*, the Temple researchers report that a drug used in the treatment of HIV also suppresses Zika virus infection. In cell and animal models, they show that the drug, called rilpivirine, stops Zika virus by targeting enzymes that both HIV and Zika virus depend on for their replication. These enzymes occur in other viruses closely related to Zika, including the viruses that cause dengue, yellow fever, West Nile fever, and hepatitis C.

"HIV and Zika virus are distinct types of RNA viruses," explained Kamel Khalili, Ph.D., Laura H. Carnell Professor and Chair of the Department of Neuroscience, Director of the Center for Neurovirology, and Director of the Comprehensive NeuroAIDS Center at LKSOM. "By discovering that rilpivirine blocks Zika virus replication by binding to an RNA polymerase enzyme common to a family of RNA viruses, we've opened the way to potentially being able to treat multiple RNA virus infections using the same strategy."

Dr. Khalili, a senior investigator on the new study, attributed the breakthrough work to a productive collaboration with Temple University colleagues, including Dr. Michael L. Klein, FRS, Laura H. Carnell Professor of Science and Dean of the College of Science and Technology at Temple; and Ilker K. Sariyer, DVM, Ph.D., and Jennifer Gordon, Ph.D., Associate Professors of Neuroscience at Temple's Center for Neurovirology.

Historically rare and isolated to parts of Africa and Asia, Zika virus is now present throughout the Americas and occurs in multiple other regions of the world. It has attracted increasing attention in recent years, owing to its damaging effects to the brain and nervous system. The virus is transmitted to humans by mosquitoes. Once in the body, it infects cells

and replicates, typically taking up residence in cells in neural tissues. In severe cases, Zika virus infection can cause an autoimmune condition known as Guillain-Barré syndrome, which culminates in muscle paralysis. Infants born to mothers infected during pregnancy may experience delays in neurological development and may be affected by microcephaly (abnormal smallness of the head).

To replicate inside cells, Zika virus requires an enzyme called non-structural protein 5 RNA-dependent RNA polymerase (NS5 RdRp). In the new study, Dr. Sariyer showed that rilpivirine suppresses Zika virus infection in cells by blocking viral replication. Using structural biology and computational studies, Eleonora Gianti, Ph.D., a research assistant professor in Dr. Klein's laboratory, was able to show that rilpivirine prevents viral replication by binding specifically to the NS5 domain.

Dr. Gordon's team carried out experiments in mice, in which animals were infected with Zika virus through their footpads, similar to the way a person becomes infected through a mosquito bite. Mice that become infected with Zika virus normally become very sick within about a week and eventually die. "We found, however, that when treated with rilpivirine, the animals survived," Dr. Gordon said. "Our conclusion is that rilpivirine disrupted the virus's usual course of infection."

Rilpivirine is one of several non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs that have been developed for the treatment of HIV infection. Experiments in which the Temple researchers tested two other NNRTIs in Zika-infected cells revealed similar effects on viral replication, with the drugs specifically inhibiting NS5 activity.

"We now have a clear path forward," Dr. Khalili said. "We have a starting point from which we can find ways to make these drugs even more potent and more effective against flaviviruses." The researchers plan to soon step up their studies to develop ways to improve the

effectiveness of NNRTIs in blocking infection with Zika virus and other flaviviruses.

Epidemics involving flavivirus infections, particularly HIV, Zika, dengue, and hepatitis C, frequently overlap geographically and temporally. "The potential applications of this work are huge," Dr. Klein added.

**More information:** Ilker Kudret Sariyer et al, Suppression of Zika Virus Infection in the Brain by the Antiretroviral Drug Rilpivirine, *Molecular Therapy* (2019). DOI: 10.1016/j.ymthe.2019.10.006

Provided by Temple University