Study demonstrates ability to remove key barrier to an HIV cure

July 25 2023, by Brian Katzowitz

Credit: Emory University

The results of a novel study presented by Emory researchers during the International AIDS Society (IAS) Conference in Brisbane, Australia, have revealed exciting findings in the pursuit of an HIV cure. The study,

led by Monica Reece, a Ph.D. candidate in Emory's Microbiology and Genetics Program, and directed by Christina Gavegnano, Ph.D., demonstrates the potential of Jak inhibitors, specifically ruxolitinib, to significantly decay the viral reservoir in people with HIV, offering a novel pathway toward long-term remission or a cure.

The HIV viral reservoir, essentially a small number of immune cells containing dormant virus integrated into the genomes of individuals who have suppressed viral replication with HIV treatment, has posed a major impediment to achieving an HIV cure. These cells are completely undetectable by the immune system because the virus is dormant. But as soon as treatment stops, the virus reactivates.

"The barrier to an HIV cure is that the virus hides inside the DNA of cells," says Gavegnano, director of the Gavegnano Drug Discovery Program and senior author on the study. "The brass ring is an agent that can eliminate these 'reservoir cells,' which would ultimately eliminate HIV from a person's body."

While Gavegnano and her Emory colleagues have shown that Jak inhibitors (Janus kinase inhibitors) could reverse the immune dysfunction caused by HIV since their discovery in 2010, questions about their impact on the HIV reservoir and the exact mechanism contributing to the immunologic improvements have remained unanswered, until now.

The data presented at IAS represented secondary results from a Phase 2a clinical trial centered on investigating ruxolitinib's effects on viral reservoirs in people with HIV during a five-week regimen, specifically in a subset of individuals with high viral reservoir levels at baseline.

The study measured integrated proviral DNA, which is the genetic material of a virus as incorporated into, and able to replicate with, the

genome of a host cell, and examined changes in total, intact only, and defective proviral DNA copies over time.

Based on a linear model of decay, the researchers estimated an astonishing 99.99% clearance of the peripheral HIV-1 reservoir in less than three years. These data provide optimism for the use of Jak inhibitors as a backbone for cure-based eradication strategies in the battle against HIV.

Reece, lead author of the study says, "These data suggest that our Jak inhibitors can not only reverse the immune dysfunction that prevents HIV-1 cure, but also significantly decay the reservoir in people living with HIV. Collectively our trial demonstrates a mechanism by which ruxolitinib, or other Jak inhibitors such as baricitinib, also extensively studied by our group, decay the reservoir, which underscores potential for cure-based therapies."

The profound impact of Ruxolitinib treatment was not limited to reservoir reduction. The study also shed light on several significant biomarkers that were altered by the drug primarily related to:

- Immune activation: Ruxolitinib exhibited the potential to modulate immune activation, which is crucial in controlling viral replication and maintaining immune health in individuals with HIV.
- Cell survival: Ruxolitinib demonstrated the ability to impact cell survival, influencing the lifespan of reservoir cells and potentially limiting viral reservoir longevity.
- Immune dysregulation: The study identified ruxolitinib's impact on immune dysregulation, offering hope for mitigating the chronic inflammation and immune dysfunction often observed in individuals with HIV.

It is important to note that the study focused on the peripheral viral reservoir and may not fully represent the entire viral reservoir within the body, including sanctuary sites where HIV can persist despite treatment.

Regardless, the findings from Emory University's study offer hope and renewed enthusiasm for efforts to unravel the complexities of HIV persistence and ultimately find a cure.

"These data are valuable because they show that Jak inhibitors can contribute to a long-term cure strategy for HIV, but they can also be used to slow the inflammatory process caused by other infectious diseases," says Vincent Marconi, MD, professor of medicine and global health at Emory University School of Medicine.

Marconi, who led the initial phase 2a trial, has already been investigating the efficacy of Jak inhibitors, like ruxolitinib and baricitinib, in patients with acute COVID and now long COVID. He continues, "using an anti-inflammatory drug to treat the effects of a virus could be revolutionary."

In addition to the data presented by Reece and Gavegnano, another presentation at IAS has shown how ruxolitinib administered to a patient following a stem cell transplant led to an undetectable viral load 20 months after stopping antiretroviral therapy, highlighting the different mechanisms in which these class of drugs could be valuable in HIV care and treatment.

Further research and clinical trials will be needed to fully understand the effects of Jak inhibitor use in HIV and other immune-suppressing conditions. Emory researchers have an extensive history of working with Jak inhibitors. Gavegnano and researcher Raymond Schinazi are listed on the issued patents as sole inventors, and they, alongside their co-investigators, have built a roadmap for tackling a variety of immunosuppressive viruses with these drugs.

Gavegnano says, "The safety and efficacy outcomes we observed in this study provide a strong foundation for further research on cure-based interventions containing a Jak inhibitor, and we hope to bring this therapy one step closer to helping people living with HIV."

Provided by Emory University