HIV discovery—biomarkers predict virus return when treatment is stopped

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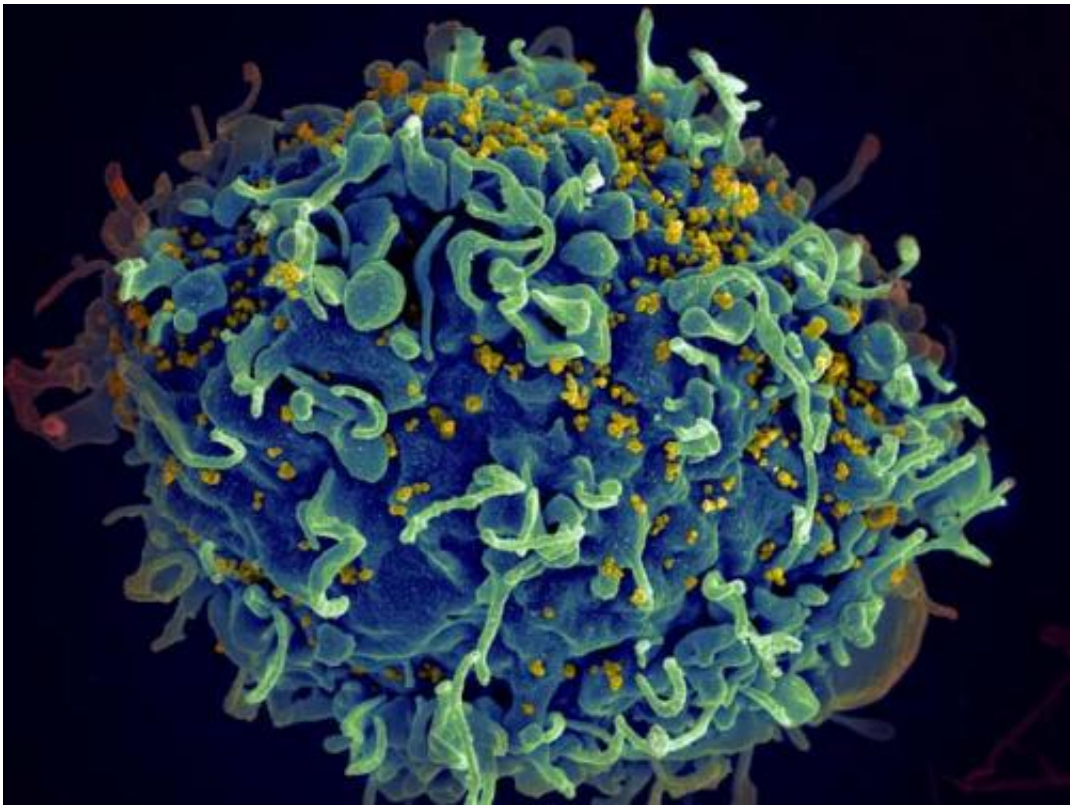

HIV, the AIDS virus (yellow), infecting a human immune cell. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Scientists are now better able to predict how quickly the HIV virus will return after individuals stop treatment following a discovery by researchers at UNSW Australia and the University of Oxford.

The significant development, resulting from a decade-long partnership between the two institutions and other international partners, opens up new avenues for understanding why the HIV virus persists in some patients and remains dormant and undetectable in others.

The study is published today in the prestigious journal *Nature Communications*.

While existing antiretroviral therapy (ART) stops the HIV virus from replicating, it does not completely remove the virus. Destroying the 'hidden' reservoirs of the virus remains one of the 'holy grails' of HIV research.

Previous research has shown the treatment of HIV with ART in the weeks following transmission produces a state of 'post-treatment control' in some patients. However, the mechanisms that induce and maintain this state of remission remain unclear.

This study provides a new window into understanding the processes that maintain viral persistence in the body, which is crucial for eradicating HIV.

Led by Oxford researcher Professor John Frater, the international research team retrospectively analysed data from a randomised study of patients with primary HIV infection involved in the SPARTAC trial. They compared the T-cells of 154 patients in Europe, Brazil and Australia who had their ART treatment interrupted after 12 or 48 weeks. T-cells play a central role in protecting the immune system.

After coming up with a shortlist of 18 immune system biomarkers, researchers discovered three of them - PD-1,Tim-3 and Lag-3 - were statistically significant predictors of when the virus would rebound.

The researchers found that high levels of these biomarkers, attached to 'exhausted' T-cells prior to patients commencing ART, were associated with earlier rebound of the virus following treatment interruption. This has never been shown before.

Former Oxford don and now Dean of Medicine at UNSW, Professor Rodney Phillips, played an instrumental role in the discovery of the association of the biomarkers with an earlier rebound of the virus.

His 2003 proposal to conduct immunology and virology of the patients receiving ART during the SPARTAC trial, provided researchers with the data they needed to make the discovery 10 years later.

"The SPARTAC study will never be able to be replicated again and it has provided us with a once-in-a-lifetime opportunity to look at the causes of viral rebound in this particular group of patients with HIV," Professor Phillips said.

"Focusing on the exhaustion markers was an important step as it has given us vital clues as to why some people are able to better control the virus after therapy has been interrupted."

UNSW Kirby Institute's Professor Anthony Kelleher, one of the study's co-authors, said understanding the mechanisms that allow HIV to remain in 'remission' is essential if the virus is to be eradicated.

"We want to be able to predict how the virus will behave before we take patients off ART to test drug therapies aimed at eradicating HIV," Professor Kelleher said.

UNSW Scientia Professor David Cooper, Director of The Kirby Institute, and Dr Kersten Koelsch were also key members of the research team.

Clinical guidelines now recommend patients continue on ART, largely as a result of another UNSW Kirby Institute-led study known as the START (Strategic Timing of antiRetroviral Treatment) clinical trial. The trial results provided conclusive evidence of the extra benefits of beginning ART early.

Immune cells with the PD1 biomarker have already been identified as a target for drugs to treat stage-four melanoma or end stage cancer. Researchers are now considering how to manipulate immune cells with the PD1 marker in their HIV research.

The study's authors are recommending that biomarkers now be considered in future research investigating how to control the HIV virus following ART.

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