The antibodies of 'post-treatment HIV controllers'

April 14 2022

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A very small percentage of people with HIV-1, known as "post-treatment controllers" (PTCs), are able to control their infection after interrupting all antiretroviral therapy. Understanding the fundamental mechanisms

that govern their immune response is essential in order to develop HIV-1 vaccines, novel therapeutic strategies to achieve remission, or both. A recent study investigated the humoral immune response—also known as antibody-mediated immunity—in some PTCs in whom transient episodes of viral activity were observed. The researchers have shown their humoral immune response to be both effective and robust, which could help to control the infection in the absence of treatment. The findings of this study were published in *Nature Communications* on April 11, 2022.

A very small percentage of people with HIV-1 and who received early treatment maintained over several years have the capacity to control the virus over the long-term when their treatment is interrupted. However, the mechanisms of this control have not been fully elucidated.

The team of researchers, led by Dr. Hugo Mouquet, director of the Laboratory of Humoral Immunology at Institut Pasteur (partner research organization of Université Paris Cité), conducted an exhaustive study in PTCs in order to characterize their humoral response (i.e. their production of B cells and specific antibodies), compared with non-controllers.

The scientists have shown that the humoral immune response profiles vary according to the activity of the virus observed in the subjects.

In PTCs who experience short episodes in which the virus resumes low-level activity after interruption of treatment, transient exposure to the viral antigens induces:

- a strong anti-HIV-1 humoral response, involving more frequent intervention of HIV-1 envelope-specific memory B cells;
- the production of antibodies with a cross-neutralizing action and which possess "effector" antiviral activities in which the innate

immune cells recognize the infected cells bound to the antibodies, thereby inducing their elimination;
- the increase in the blood of atypical memory B cells and subpopulations of activated helper T cells.

This specific, multifunctional, and robust humoral response could help to control their infection in the absence of treatment.

However, other PTCs in whom the virus continuously remains undetectable after treatment interruption do not develop a strong humoral response. The control mechanisms in these patients continue to be investigated in the VISCONTI study.

The discovery of these two types of humoral immune response, which depend on the profile of the PTCs, sheds new light on the phenomenon of HIV control. For Dr. Mouquet, researcher at Institut Pasteur and principal investigator of the study, "these findings show that early antiretroviral treatment can facilitate the optimal development of humoral immune responses, in some cases countering viral rebound after treatment interruption." The example of the immune response of the PTCs having short episodes of "awakening" of the virus could even inspire novel therapeutic or vaccine strategies.

The "post-treatment controllers" whose samples were used for this research are part of the VISCONTI (Viro-Immunological Sustained COntrol after Treatment Interruption) study, coordinated by Dr. Asier Sáez-Cirión (Institut Pasteur) and Dr. Laurent Hocqueloux (Orleans Regional Hospital) and supported by ANRS for several years. This is the largest cohort of long-term "post-treatment controllers".

It includes 30 patients who had received early treatment that was maintained for several years. Upon interruption of their antiretroviral therapy, they are able to control their viremia for a period exceeding 20

years in some cases. VISCONTI therefore provides the proof of concept of a possible and sustained state of remission for HIV-1-infected patients. It has paved the way for the development of novel therapies that target remission from the infection—if not its eradication. The objective is to enable people living with HIV-1 to stop their antiretroviral treatment on a lasting basis, while maintaining viremia at the lowest level and avoiding the risk of transmission of the virus.

More information: Luis M. Molinos-Albert et al, Transient viral exposure drives functionally-coordinated humoral immune responses in HIV-1 post-treatment controllers, *Nature Communications* (2022). DOI: 10.1038/s41467-022-29511-1

Provided by Pasteur Institute