Giving antibodies to infant macaques exposed to an HIV-like virus could clear infection

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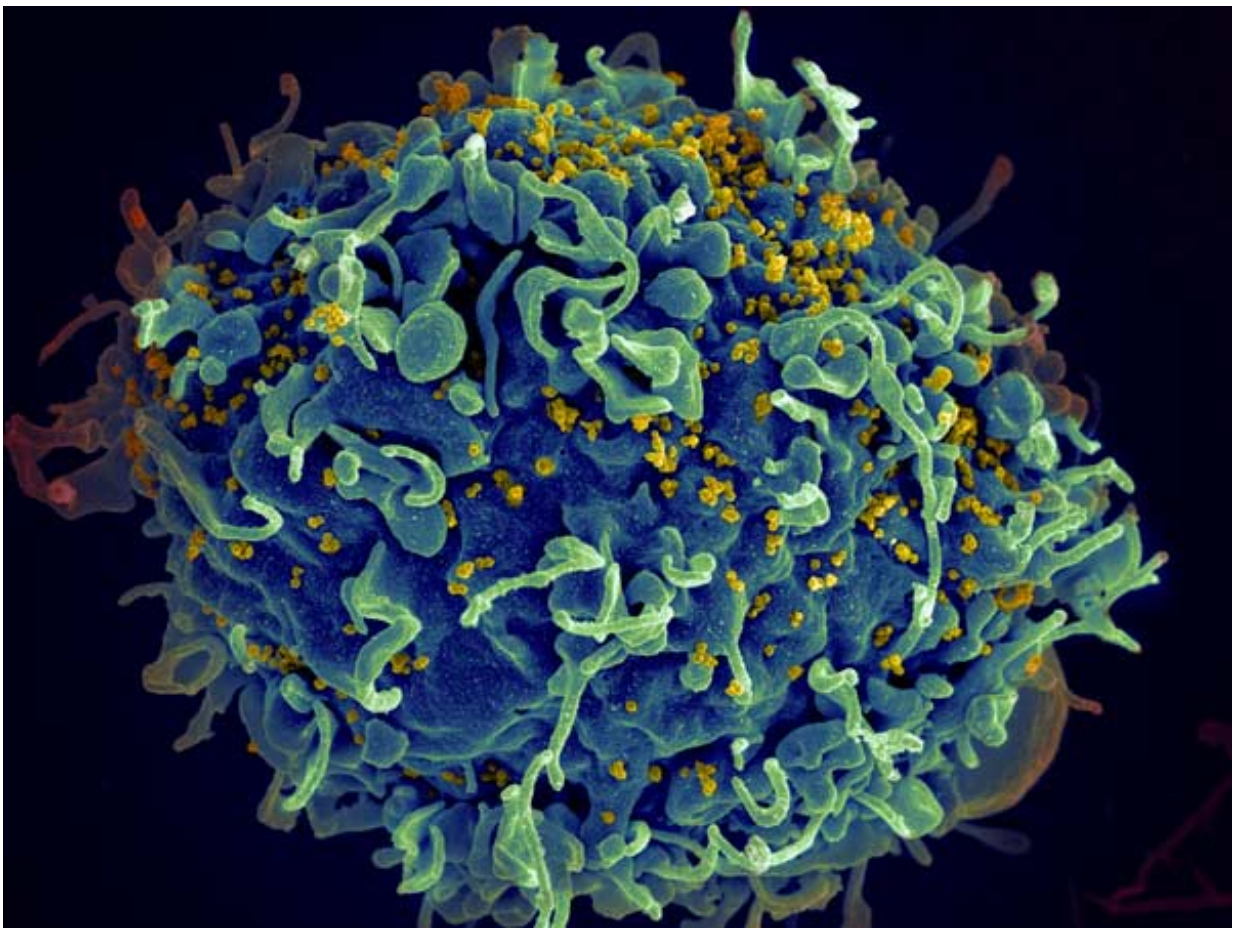

HIV (yellow) infecting a human immune cell. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Scientists at the Oregon National Primate Research Center today revealed that infant rhesus macaques treated with antibodies within 24 hours of being exposed to SHIV, a chimeric simian virus that bears the HIV envelope protein, were completely cleared of the virus. The study, published today in *Nature Medicine* shows that antibodies given after a baby macaque has already been exposed to SHIV can clear the virus, a significant development in the HIV scientific community.

SHIV-infected nonhuman primates can transmit SHIV to their offspring through milk feeding, just as humans can transmit HIV from mother to child through breastfeeding and during childbirth (and only rarely during pregnancy). In humans, a combination of measures for mothers and infants, including antiretroviral therapy (ART), Cesarean section delivery and formula feeding (rather than breastfeeding), have decreased the rate of mother-to-child HIV transmission from 25 percent to less than 2 percent since 1994. Despite this decrease, approximately 200,000 children are infected with HIV each year worldwide, primarily in developing countries where ART is not readily available.

"We knew going into this study that HIV infection spreads very quickly in human infants during mother-to-child transmission," said Nancy L. Haigwood, Ph.D., senior author of the paper, and director and senior scientist, Oregon National Primate Research Center at Oregon Health & Science University. "So we knew that we had to treat the infant rhesus macaques quickly but we were not convinced an antibody treatment could completely clear the virus after exposure. We were delighted to see this result."

Haigwood and colleagues administered the anti-HIV-1 human neutralizing monoclonal antibodies (NmAb) subcutaneously on days 1, 4, 7 and 10 after the macaques were exposed to SHIV orally. The SHIV virus was found in multiple body tissues on day 1 in macaques without antibody treatment. Conversely, they observed an immediate impact of a

single dose of antibodies at the start of the infection, with a significant difference in treated versus non-treated macaques. Early short-term administration of powerful antibodies effectively cleared the virus by day 14, with no virus detected at this time. Using highly sensitive methods, they did not detect the virus in any part of the body in 100 percent of the antibody-treated infant macaques for at least six months.

Typically, HIV infection rapidly expands and spreads in humans to local draining lymph nodes before disseminating throughout the entire body one week after a person is infected. This study showed that, at least in this model system of oral SHIV exposure in newborn macaques, virus replication is detected in lymphatic tissues 24 hours after exposure and is not locally restricted, as has been suggested previously for humans, due to delays of 5 to 7 days before detection in the blood.

The study showed that: 1) antibodies delivered subcutaneously are swiftly distributed to blood and tissues and maintain neutralizing activity at various sites, and, 2) that antibodies are effective at clearing the virus, a different mechanism than that of ART, which is a combination of several antiretroviral medicines used to slow the rate at which HIV makes copies of itself in the body.

"Other nonhuman primate studies with antiretroviral therapy suggest that treatment as early as three days after infection is too late to prevent establishment of the HIV reservoir," said Jonah B. Sacha, Ph.D., study co-author and assistant scientist, Oregon National Primate Research Center at OHSU. "So using antibodies to clear the virus after infants have already been exposed could save thousands of lives" if the approach works in human infants.

The researchers noted that treating human babies with ART during the last month of gestation, the few days after delivery, and during breastfeeding timeframes, is recommended. However, risks remain,

including toxicities associated with long-term ART use, the development of drug-resistant viral variants, and lack of access to prenatal care prior to delivery.

This discovery indicates that using new methods, such as antibodies, to limit infection after exposure in newborns could be advantageous.

The study authors acknowledge that several relevant questions remain unanswered for treatment of HIV-infected newborns and children born to HIV-positive mothers. These include practical and cultural issues of treating breastfeeding mothers and babies, if the antibodies will work in human infants exposed to HIV, as well as what the optimal antibody formulations will be.

Clinical trials in which HIV-exposed newborns are treated with antibodies have begun in the U.S. and South Africa, following a phase I clinical trial in HIV-negative adults that showed the antibodies to be safe and well-tolerated in these individuals.

The authors' findings help define the window of opportunity for effective treatment after exposure to HIV during birth. If these primate model results can be applied to human beings in a clinical setting, researchers are hopeful that treating infants who have already been exposed to HIV within 24 hours may provide protection from viral infection, even in the absence of ART.

More information: Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques, *Nature Medicine*, DOI: 10.1038/nm.4063

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