# Newly defined biomarker may accelerate clinical trials for vaccines to prevent HIV-1 infection

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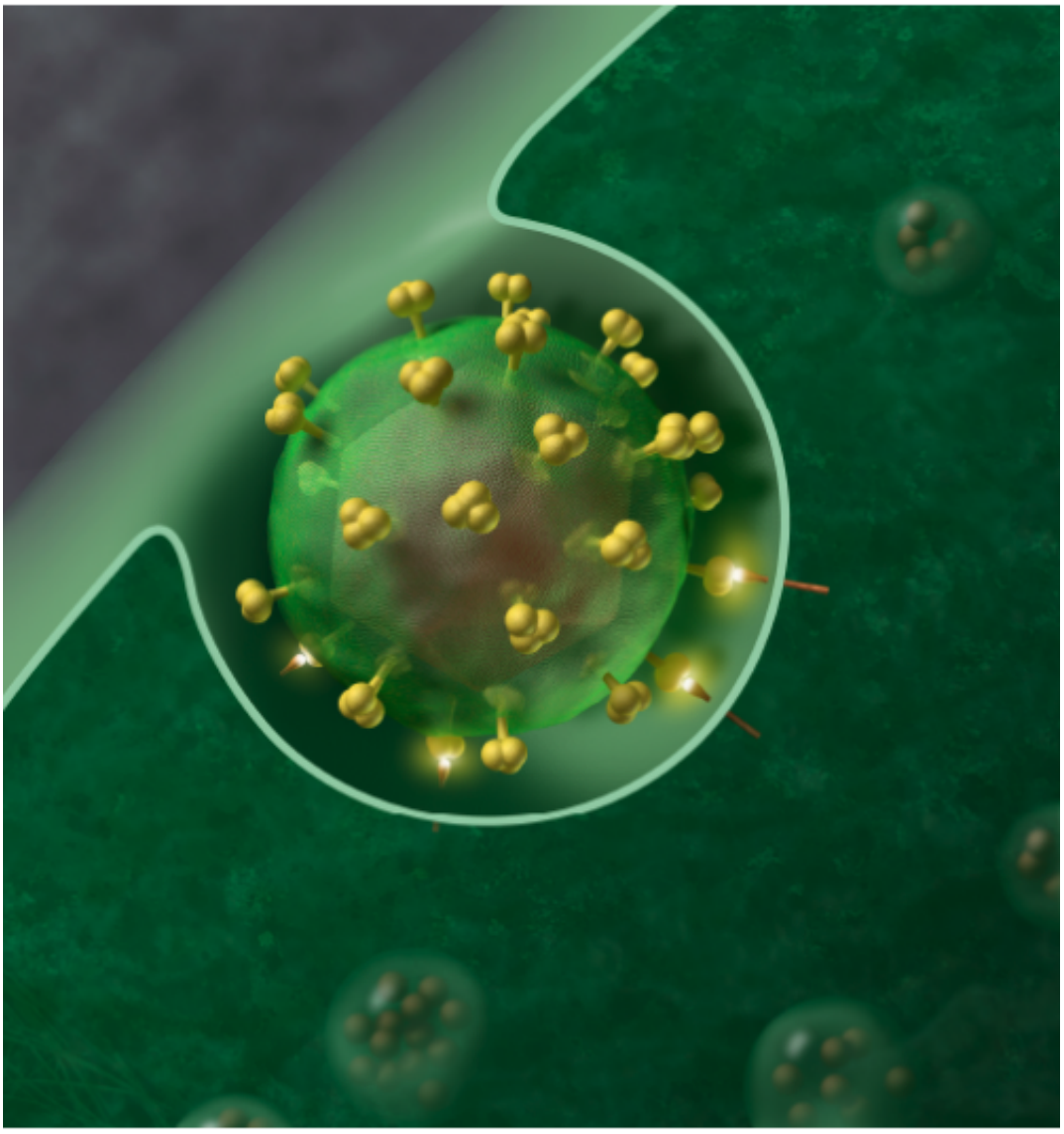

HIV-1 Virus. Credit: J Roberto Trujillo/Wikipedia

A study published in the Aug. 22, 2022, issue of *Nature Medicine* identifies a new biomarker that appears effective as a surrogate endpoint to reliably predict the ability of broadly neutralizing monoclonal antibodies to prevent acquisition of HIV-1, the most common type of the virus that causes AIDS. Broadly neutralizing antibodies (bnAbs) are defined by their ability to neutralize multiple genetically distinct viral strains.

Findings from this study build on the proof-of-concept Antibody Mediated Prevention (AMP) trials published in March 2021 showing that a bnAb called VRC01 was effective in preventing the acquisition of some—but not all—HIV strains. Seventy percent of strains circulating in regions where the studies were conducted—sub-Saharan Africa, the U.S. and South America—were resistant to VRC01, and the original report noted no statistical difference between the VRC01 arms and the placebo arm in overall prevention of HIV acquisition.

"A single HIV-1 broadly neutralizing monoclonal antibody, such as VRC01, will not be sufficient to provide high protection against HIV-1 acquisition because many strains are resistant. Therefore, bnAb cocktails will be needed, and although there is a rich pipeline of these antibodies under development, we first needed a biomarker that would enable us to compare cocktails and select the best candidates to advance to efficacy trials," said Dr. Peter Gilbert, one of the paper's co-first authors. He and co-first author Dr. Yunda Huang are researchers with the HIV Vaccine Trials Network (HVTN), based at Fred Hutchinson Cancer Center in Seattle. The study was conducted with collaborators from the HIV Prevention Trials Network (HPTN), based at FHI 360, Durham, North Carolina.

Gilbert said a useful biomarker must also be validated as a surrogate

endpoint to reliably predict the prevention efficacy level of an HIV-1 bnAb cocktail. This would permit expedited approval of different cocktails without requiring long and expensive efficacy trials. According to results from this study, the newly defined biomarker, called PT80, appears to meet those requirements, which predicts the 80% neutralizing antibody titer of a bnAb recipient's blood sample at a given time to a given virus.

"In other words, PT80 quantifies the 'killing power' of a bnAb in a blood sample at a given time point against a specific HIV-1 strain," said Dr. Larry Corey, AMP Protocol Chair and Principal Investigator, HVTN Leadership Operations Center. "Our study showed that PT80 is likely to be highly successful as the sought-after biomarker and surrogate endpoint for future monoclonal antibody studies."

The HVTN and HPTN expect to leverage these study results in planning and seeking approval for an AMP-sequel, large-scale efficacy study.

"This research sought to provide validation data for the PT80 biomarker for the specific HIV-1 bnAb VRC01, but our team will further study validation of this biomarker for non-VRC01 cocktails," said senior author Myron Cohen, M.D., AMP Protocol Chair, HPTN Principal Investigator, and Director of the Institute for Global Health and Infectious Diseases at the University of North Carolina at Chapel Hill. "One of our priorities is the study of novel candidate HIV-1 vaccine regimens that, through iterative refinement, will identify those that induce antibodies to broadly neutralize most strains of HIV-1 for at least six to 12 months post-vaccination. This study predicts that such a vaccine would be effective at preventing HIV-1 acquisition."

In the primary AMP trials paper, a biomarker called IC80 was able to measure the susceptibility of an exposing virus to the monoclonal antibody given in the trial. This assay is done in a test tube with the

infecting strain. But IC80 contains no information about the quantity of bnAb in an individual's blood sample. PT80 allows analysis of bnAb concentrations measured over time.

This study:

- Codified HVTN/HPTN's use of PT80 as a primary study endpoint for Phase 1 clinical studies of HIV-1 bnAb cocktails for ranking and selecting bnAb regimens.
- Showed similar results for the PT80 biomarker in two diverse contexts: 1) sub-Saharan African women in a subtype C HIV-1 epidemic, and 2) men who have sex with men and transgender persons in Peru, Brazil, Switzerland and the U.S. in a predominantly subtype B HIV-1 epidemic. This replication in two study and virus populations strengthens the generalizable use of this biomarker.
- Partially validated results from nonhuman primate studies showing that the PT80 biomarker is related to prevention efficacy in a similar way for VRC01 recipients in the AMP trials as for nonhuman primate recipients of bnAbs in virus challenge models. This indicates that previous nonhuman primate studies of VRC01 and other bnAbs did not overpromise in what level of protection could be achieved with VRC01 in the AMP efficacy trial.
- Confirmed that PT80 is a very good predictor of neutralizing antibody titer. Neutralizing antibody titer has been successfully used as a surrogate endpoint for approval and use of vaccines against many different pathogens. Through the COVID-19 Prevention Network, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), HVTN scientists have shown that neutralizing antibody titer is supported to be a useful surrogate endpoint for occurrence of symptomatic COVID-19 in all five COVID-19 vaccine efficacy trials that have been

analyzed. The researchers anticipate that PT80 developed in this study will have similar utility in the HIV-1 prevention field.

"Our modeling predicts that currently available triple cocktail HIV-1 bnAbs, administered every four to six months, would have high prevention efficacy of approximately 90%, which, once verified in an efficacy trial, is promising for regulatory approval as a new modality for HIV-1 prevention," Huang said. "Communities generally favor diversity in HIV prevention options, recognizing that one option doesn't work for everyone. For example, some people prefer a bnAb over antiretroviral-based prevention, such as PrEP, due to potential advantages in safety and side effects."

The two AMP studies (HVTN 704/HPTN 085 and HVTN 703/HPTN 081) opened in 2016 and successfully enrolled 4,623 participants. The studies are sponsored and funded by NIAID, part of the National Institutes of Health, and were conducted jointly by the HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN). The NIAID Vaccine Research Center (VRC) isolated VRC01 in 2010 from the blood of a person living with HIV and subsequently manufactured the antibody for the AMP studies. Data from the AMP studies were first reported at a press conference hosted by the 4th International HIV Research for Prevention Conference (HIVR4P) on Jan. 26, 2021. The *New England Journal of Medicine* published these results in March 2021.

There are still more than 1.7 million new cases per year of HIV globally; more than 75 million people have acquired HIV and more than 32 million people have died from AIDS-related illnesses since the pandemic began. The need for a safe and effective preventive HIV vaccine and other HIV prevention technologies remains as urgent as ever.

**More information:** Peter Gilbert, Neutralization titer biomarker for

antibody-mediated prevention of HIV-1 acquisition, *Nature Medicine* (2022). DOI: 10.1038/s41591-022-01953-6.
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