

Researchers Track the Mutations That Allow HIV to Escape Broadly Neutralizing Antibodies

Some 1% to 5% of people with HIV naturally produce broadly neutralizing antibodies that are active against most virus strains.

May 13, 2026 By Rockefeller University

Broadly neutralizing antibodies (bNAbs) are among the most promising new treatments for HIV, offering the potential to forego the traditional daily dose of antiretroviral drugs. In one recent [clinical study](#) of bNAbs identified and developed into therapies at Rockefeller University, participants who received a single dose of two bNAbs maintained a nearly undetectable viral load for up to 20 weeks, and a third did so for about a year. These outcomes suggest a potential future of treatment-free, long-term control of the virus.

However, HIV-1 is extraordinarily genetically diverse and highly adept at acquiring resistance to neutralizing antibodies. The pathways by which the virus escapes bNAbs remain incompletely understood across diverse HIV-1 strains. A better understanding of how different strains respond to these emerging therapies is critical as the use of bNAbs expands.

Now Rockefeller scientists have established the most comprehensive view to date of how HIV-1 can escape bNAbs. Using thousands of parallel viral selection experiments combined with bioinformatic analysis and experimental validation, researchers in the [Laboratory of Retrovirology](#), co-led by [Paul Bieniasz](#) and [Theodora Hatziioannou](#), discovered viral mutations that make HIV-1 strains resistant to two bNAbs, 3BNC117 and 10-1074. They [published](#) their results in *Nature Microbiology*.

However, not all resistance-creating mutations are equal: Some require merely a single amino acid change, while others need more complex molecular machinations.

“We found that most viral strains can escape bNAb neutralization, but there’s substantial variation in the likelihood that they will and the mechanisms that enable it,” says first author Alex Stabell, an infectious disease physician and clinical scholar at Rockefeller.

“Knowing how different strains of the virus respond to leading bNAb therapies will greatly improve our ability to anticipate whether a particular therapy will be effective for individual patients,” says

Bienasz. “And if we can identify broadly neutralizing antibodies that the majority of strains have great difficulty escaping from, we can create more robust treatments.”

Prevention and control

HIV-1 is an exceptionally adaptable virus that is waging a small-scale evolutionary battle with the antibodies produced by the people it infects. Unlike the measles virus, whose capitulation to the human immune system has led to the overwhelming success of a vaccine that largely hasn’t changed in decades, HIV-1 has proved itself impervious to prevention via vaccination. Prevention by other means, including antiretroviral drug therapy, has long been the best option.

However, some 1% to 5% of people infected with HIV-1 have a superpower: They naturally produce broadly neutralizing antibodies that are active against most HIV-1 strains. It’s from these individuals that Rockefeller’s Michel Nussenzweig and Marina Caskey isolated the bNAbs they coined 3BNC117 and 10-1074. That [developed into a treatment](#) that uses both antibodies together because they engage with different parts of the viral envelope—and has yielded promising results.

The HIV-1 experts in the Bieniasz-Hatziioannou lab wanted to investigate how different HIV-1 strains stacked up against these bNAbs. Only a handful of resistance mutations have been identified in a limited number of viral strains. The researchers wanted to expand that number to represent global viral diversity.

“No one has attempted to do this at such a scale before,” Hatziioannou says.

Experimental pipeline

Building on their groundbreaking work with SARS-CoV-2—in which they documented how the notorious “spike” on the COVID viral envelope [evolved](#) in response to neutralizing antibodies found in patients—Stabell developed an approach that would allow them to study the mutational pathways to escape among 15 strains of HIV-1 sourced from around the globe. The goal was to pinpoint the mutations that were contributing to each strain’s propensity to develop resistance.

Stabell devised a pipeline that began by growing large amounts of virus in cell culture. Replication errors naturally create a diverse population of viruses, some of which will, by chance, carry resistance mutations. He used these bulk populations to seed more than 7,000 parallel selection experiments with varying concentrations of bNAbs. Viruses that were able to spread in the presence of the bNAbs were isolated and sequenced. Custom bioinformatic processing gave a list of putative resistance mutations, which were then experimentally validated for each viral strain.

Battling mutations with drug combinations

Using this method, which they dubbed RISC (resistance identification via selection and cloning), the team found more than 100 bNAb escape mutations across the 15 viral strains tested, dramatically expanding the known number. Surprisingly, they found that in most cases, a single amino acid change may be enough to confer resistance. That turned out to be true for 12 of the 15

viruses tested against the 3BNC117 antibody and for all nine tested against 10-1074.

“It was striking that it’s actually quite easy for most HIV-1 strains to escape these special antibodies,” Bienasz says. “But it’s not true for all strains—a handful Alex worked with needed multiple amino acid substitutions or unusual ways to replicate in order to escape.”

“The genetic barrier to resistance was higher for these viruses,” Stabell adds. “One of the goals of therapy these days is not simply to have therapies that are transiently effective, but to have this high genetic barrier.”

They also identified a surprising number of mutations occurring outside the epitope on the viral envelope recognized by bNAbs that target the CD4 binding site, such as 3BNC117. (10-1074 aims for a more mutable envelope target, which may help explain why it’s easier to escape.)

“These were quite prominent and unexpected,” says Hatzioannou. “No one would have predicted these would affect bNAb sensitivity.”

In the future, the team will use Stabell’s method to identify to discover resistance mutations to other bNAbs as well as to combinations of them.

“HIV-1 mutates so fast and the diversity in the population is already quite enormous, so we’ve long known that a multidrug approach is the best course of treatment,” she says. “We hope to identify combinations that potentially raise the genetic barrier to resistance and are therefore more effective.”

This [news release](#) was published by the Rockefeller University of May 11, 2026.