Early Long COVID Trials of Paxlovid and Monoclonal Antibodies Failed, but the Treatments Still Have Potential

While three early studies did not see health improvements, further trials are getting more intentional in targeting viral persistence.

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Key points you should know:

- Three prominent clinical trials targeting viral persistence in long COVID with short treatment courses have not found that the drugs under study, Paxlovid and a monoclonal antibody, led to improved health for participants.
- Viral persistence, the hypothesis that SARS-CoV-2 or pieces of it continually replicate in the body and lead to chronic symptoms, has been a challenge to study.
- In an ideal scenario, a trial would specifically recruit participants with viral persistence markers and then measure changes in those markers. This hasn't been feasible in the studies done so far.
- Next-round clinical trials, such as one recently started with the monoclonal antibody sipavibart, are learning from the first round of studies, while researchers who conducted the initial studies continue to analyze biospecimens from participants.
- Future trials may test novel antivirals and monoclonal antibodies currently in development. At the same time, researchers are working to better measure viral persistence.

At the University of California, San Francisco's Pride Hall, the labs and exam rooms where scientists conduct cutting-edge long COVID research are a short walk from a space called Ward 5B. Established in 1983, this ward was the first-ever inpatient clinic dedicated to HIV/AIDS.

Today, Ward 5B is marked by a plaque that commemorates the clinicians, caregivers, and patients who offered and received care for the devastating disease in that space. Now that ward and nearby facilities host clinical trials for continued HIV/AIDS research as well as long COVID studies.

Michael Peluso, an infectious disease clinician and researcher who leads much of that cutting-edge long COVID research, pointed it out to me as we walked through the center one afternoon in May. A couple of weeks earlier, at an online symposium hosted by the PolyBio Research Foundation, he had first shared preliminary results from a novel clinical trial that he and his colleagues conducted, which tested a monoclonal antibody called AER002 for long COVID.

The trial was unsuccessful according to its primary outcome measure: it found no significant difference in health improvements between people who received the treatment and those who received a placebo. But Peluso wasn't discouraged. And it was hard not to feel the same way when I remembered the long years between Ward 5B's first patients and the treatment and prevention regimens available for HIV/AIDS today.

Like the AER002 trial, two clinical trials at Yale and Stanford that tested Paxlovid as a long COVID treatment also didn't find that the antiviral helped improve people's health. Taken together, these studies suggested that repurposing acute COVID-19 treatments for long COVID was not an easy solution to this complex disease, Peluso told me — at least, not at the doses and durations of these treatments scientists have tested so far.

"I think the first round of trials answered the question about whether it would be easy to hit a home run, and the answer was no," he said. He and other researchers expected that outcome, though they had hoped for a different one.

Still, there is much to learn from those early trials — namely, how scientists should design the next ones. Now that researchers have determined that a short course of an antiviral like Paxlovid isn't enough to improve long COVID, they are focused on more specific questions. Which treatments, taken at which times and for how long, are best suited to address viral persistence? How do we know when viral persistence has been addressed? How do we pair biological measurements with those showing improvements in people's quality of life?

Some trials that will help answer these questions have already started, like one at Nova Southeastern University (NSU) in Florida examining the preventative monoclonal antibody sipavibart. Others are likely to start in the coming months and years. Long COVID researchers are also collaborating across research institutions and disciplines to answer these questions more efficiently through venues like PolyBio's Long COVID Research Consortium and the Keystone Symposia meeting, happening this week [August 10-13] in Santa Fe, New Mexico.

These first- and second-round antiviral and monoclonal antibody studies are set to offer major insights into the underlying biology of long COVID and more specific ideas for how to treat it, said Jon Douglas, a patient-advocate who closely follows trials. Further options, such as testing drugs for longer and in combination, will offer "an unlimited playground for clinical trials researchers in the next five years or so," he said.

Targeting viral persistence is complex

Trials testing Paxlovid and monoclonal antibodies are based on a long-standing theory about how viruses like SARS-CoV-2 can cause chronic symptoms: viral persistence. The idea is that the coronavirus, its genetic material, or specific components like the virus's spike protein continually copy themselves inside a person's body, causing dysfunction across different body parts and systems.

If that's the case, the hypothesis goes, when someone with long COVID takes a therapy designed to combat SARS-CoV-2, the drug should reduce those viral copies and cut down on the dysfunction, leading to improvement in symptoms.

This idea actually predates COVID-19 and long COVID, said Stephen Smith, a patient-advocate who follows clinical trials. Researchers and advocates have long considered it an "obvious source" of post-viral illnesses like myalgic encephalomyelitis (ME), he said. But ME researchers had a hard time pinning down that source because people with the disease have a range of initial infections and other potential disease triggers.

With long COVID, on the other hand, researchers know that all symptoms can be traced back to a SARS-CoV-2 infection, while cases of similar symptoms after vaccination suggest the virus's spike protein may be enough on its own to wreak havoc. Following that logic, COVID-specific treatments like Paxlovid and monoclonal antibodies are clear candidates for treatment.

But the ongoing research into viral persistence suggests that it's not so easy. One major challenge is timing. Antivirals are most effective when people take them immediately after getting sick, but that is generally not what happens in long COVID trials.

Most studies so far tying viral persistence to long COVID symptoms focus on "that first year" after someone's infection, Peluso said. Many participants in trials have been ill for at least two years; many people with the disease have now passed their five-year anniversaries.

Research also hasn't yet pinned down exactly how viral pieces are replicating, said Nancy Klimas, director of the Institute for Neuro-Immune Medicine at NSU and the lead researcher on the sipavibart trial. If the entire SARS-CoV-2 virus persists, as the HIV virus does, that would be more challenging to suppress through treatments than if only its spike protein or its genetic material does. For HIV, a single antiviral drug used on its own "didn't work," she said.

Plus, it's difficult to identify which potential trial participants might still have viral reservoirs. Some research, like that of Sara Cherry and colleagues at the University of Pennsylvania (UPenn), suggests that viral pieces might be doing the most damage in areas that aren't easy for a standard lab test to measure — or for a standard antiviral to reach. In a presentation at the PolyBio symposium in May, Cherry explained that the gastrointestinal tract may be a likely hiding spot for SARS-CoV-2 reservoirs, while Paxlovid and Lagevrio (molnupiravir), another COVID-19 antiviral, are more effective in the lungs.

A May 2025 paper by Peluso, Cherry, PolyBio founder Amy Proal, and other members of the organization's consortium, published in The Lancet Infectious Diseases, describes these challenges along with other considerations for viral persistence–focused trials. In an ideal scenario, the authors write, trial investigators "would recruit only participants confirmed to harbour a SARS-CoV-2 reservoir and assess changes in reservoir measures before and after the intervention." But both such recruitment and measurement are difficult without a clear biomarker, which the field currently lacks.

Another consideration is that damage to areas like the gut microbiome and immune system builds up over time. So for those people who have had symptoms for years, even if a course of Paxlovid were to clear all remaining viral reservoirs, other issues like inflammation, autoimmunity, and reactivated viruses might still persist.

"None of us know the right time, none of us know the right dose, none of us know the biophysical parameters of, where is this reservoir?" said Marc Elia, Chairman of the Board of biotech company Invivyd, which recently announced it will test its monoclonal antibody therapy Pemgarda (pemivibart) for long COVID.

But, as Elia said, while we don't have perfect biomarkers to study viral persistence, "we don't have nothing, either." Studies from UCSF, UPenn, and other PolyBio consortium members consistently find that around 25% to 35% of people with long COVID have viral fragments in their blood or immune markers of persistence, Peluso said. Klimas also noted these findings, saying that she and her colleagues designed the sipavibart trial to pick up a potential similar rate of success with the therapy.

Early trials as "proof of concept"

At the time when both initial Paxlovid studies and UCSF's study of AER002 started, there were very few clinical trials happening for long COVID. In August 2023, out of nearly 400 long COVID studies listed on ClinicalTrials.gov, only 12 were testing pharmaceutical interventions, according to an editorial published at the time in The Lancet Infectious Diseases.

These studies "established proof of concept for the fact that rigorous clinical trials could be performed for this condition in the first place," Peluso said, recalling hesitation from the Food and Drug Administration when long COVID trials were first proposed. The early trials also established that Paxlovid and monoclonal antibodies are safe treatment options in research settings, which is an important step for larger studies.

They are safe treatment options — yet not overwhelmingly effective ones, at least not with short courses. Both Paxlovid trials tested the drug for 15 days, longer than the standard five-day course for acute COVID-19 but fairly short in the grand scheme of chronic illness.

"I don't think anyone was surprised at the results" of those two trials, Douglas said, given their short timeframes as well as reports in the long COVID community from people who had tried Paxlovid on their own. For some, the antiviral leads to a brief relief from some symptoms, followed

by a later return to baseline, he said.

One case series, published in Nature's Communications Medicine in January 2025, shared the experiences of 12 people who tried Paxlovid for extended time periods, ranging from seven to 30 days. The study showed that Paxlovid likely helped some participants, but not others, lead author Alison Cohen, an epidemiologist at UCSF and member of the Patient-Led Research Collaborative, said.

Commenting on the Yale and Stanford trials, she wrote that the two trials may have included a similar "heterogeneity of patient responses." Cohen added: "If the (currently unknown) truth is that [Paxlovid] benefits some patients with long COVID and not others … these clinical trials may have been statistically underpowered" — meaning they didn't include enough people, or perhaps not enough people with active viral reservoirs.

Stanford's trial included 155 participants, while Yale's included 100. Neither trial was particularly selective beyond recruiting people who had had long COVID symptoms for around three months. UCSF's AER002 study was smaller, with 36 participants, and recruited people whose long COVID symptoms followed an infection with a variant against which the drug is effective.

None of these studies followed the "ideal scenario" of recruiting participants who have confirmed SARS-CoV-2 reservoirs and then specifically measuring those reservoirs before and after treatment. Bornali Bhattacharjee, one of the researchers who led Yale's trial, noted that lack of specific recruitment and the short duration as two "possible interpretations" behind why the study did not find improvement in symptoms.

But both Yale and UCSF's teams are further studying specimens collected from their trials' participants. Peluso and his colleagues are working on "detailed exploratory analyses," which will be a significant part of a paper about the AER002 results that he said will likely be available as a preprint within the next two months. These analyses include looking for changes in viral persistence measures and for biological signatures specific to people whose symptoms improved with the treatment. Bhattacharjee wrote that Yale's team has completed a similar analysis and a scientific paper with those results is in progress.

The Yale study was unique in using a decentralized format. Rather than requiring all participants to come to New Haven, the researchers recruited people from across the U.S. and conducted the trial remotely.

"I never had to leave the house" except for one or two blood draws, said Amy Engebretson, a physician with Long COVID and participant in Yale's study. Engebretson, who also contributes to the Long COVID Weekly newsletter, noted that this type of study format makes research more accessible. People with more severe symptoms as well as those living in more rural areas, far from research centers, can participate in decentralized trials.

While Engebretson appreciated being part of Yale's study, she noted one potential issue in Yale's and Stanford's trial design. In both studies, participants in the placebo groups took the drug ritonavir, which is the part of the Paxlovid regimen that provides the drug's distinct metallic-taste side effect. Ritonavir is not designed to specifically combat SARS-CoV-2 as nirmatrelvir (the other pill in the regimen) is, but it does have antiviral properties on its own, which may contribute to symptom relief for some people.

"That actually happened with me," Engebretson said. "In fact, I'm still taking this drug [ritonavir] because it improved my symptoms quite a bit." If this improvement happened with other people in the trials, it could have muddled their results, she said. Bhattacharjee acknowledged that ritonavir may have interfered with the Yale trial's results.

Understanding who responds and why

If acute COVID-19 treatments help some people with long COVID but not everyone, then, Cohen said, "The next step for research would be to try to identify which people experience benefits and why."

Each new trial will offer new insights to this end. In the near future, researchers are looking forward to results from two more Paxlovid trials: one from the Karolinska Institute in Sweden and one from the National Institutes of Health's RECOVER program. Both trials have finished collecting data, according to their pages on ClinicalTrials.gov, but have not yet shared their findings.

RECOVER-VITAL included nearly 1,000 participants, a much larger group than the Yale and Stanford studies. It tested a 15-day Paxlovid course as well as a longer one of 25 days. That might still not be long enough for meaningful symptom relief, but the longer course, combined with the larger sample size, may predispose this study to pick up signals about who the drug helps.

"I'm super doubtful" that RECOVER-VITAL's results will be different from the prior studies given the similarities in their study designs, Engebretson said. She wants to see future trials try to "chronically suppress" viral persistence through testing longer drug courses as well as use different placebos. Both RECOVER-VITAL and the Karolinska study are using ritonavir in their placebo arms.

A representative of the Duke Clinical Research Institute, which leads RECOVER-VITAL, wrote in an email that the team is "currently analyzing the data but [does] not yet have a clear timeline about when the results will be ready."

Meanwhile, new research with monoclonal antibodies is just getting started. These drugs may be better suited to tackle viral persistence than Paxlovid, said Elia, from Invivyd. Paxlovid and similar antivirals mainly work to stop the virus from replicating over a short-term period, while monoclonal antibodies "can essentially sit over the very long term" and continually "try to pull [the virus] out and eliminate it," he explained.

Sipavibart, the monoclonal antibody now under study at NSU, is designed to protect people for six

months. Unlike Paxlovid, it's a preventive treatment and is currently approved in the E.U., Canada, and Japan as a COVID-19 precaution option for immunocompromised people — similar to Pemgarda in the U.S. NSU's phase 2 trial will include about 100 people, who will receive either the monoclonal antibody or a placebo and participate in follow-up testing for 24 weeks afterward.

Study participants started receiving the drug this summer, according to Klimas. "I think we picked the right product, I think that we have the right group, that we're measuring the right stuff, and we'll know from this study if it's worth pursuing or not," she said.

With "measuring the right stuff," she referred to the trial's long list of outcomes measures. The study's page on ClinicalTrials.gov lists more than 20, including several surveys to identify how the treatment impacts participants' symptoms and quality of life, measurements taken during and after a six-minute walk test and the NASA Lean Test, and more. Klimas and her colleagues are also collecting samples for a biorepository, which other researchers could use to examine biological changes before and after treatment.

Klimas has explained the extensive testing to participants by saying, "We have to do that many so that we can do much fewer in the future studies." Peluso and his colleagues at UCSF are working along the same lines as they analyze the AER002 study results and plan further trials. The two groups have similar philosophies, "including a robust set of secondary and exploratory analyses that can provide leads to what should be done in the future, even if the top-line result turns out to be negative," he wrote, commenting on the NSU trial.

Both Peluso and Klimas acknowledge this approach can be taxing for participants and inaccessible to those with more severe symptoms. But they said it's vital to setting better standards for the future, as trials like these may identify specific tests that are well-suited to track improvement.

Elia is thinking about similar issues through collaboration with the new SPEAR Study Group, an initiative that Invivyd launched last month to study Pemgarda for long COVID and post-vaccine syndrome. The initiative responds to anecdotes and case series from researchers and patients "who seem to be reporting a pretty meaningful quantum of improvement from long COVID symptoms" following Pemgarda treatment, Elia said.

The study group includes Peluso, Amy Proal, David Putrino from Mount Sinai, and Akiko Iwasaki from Yale University. Notably, the researchers plan to study people whose chronic symptoms started after vaccination in addition to those whose symptoms followed SARS-CoV-2 infection, as Pemgarda may help both groups, Elia said.

Looking ahead to next-generation treatments

Current and recent clinical trials targeting viral persistence

Trial	Drug tested	Phase	Lead institution	Status (as of August 2025)
RECOVER-VITAL	Paxlovid (15 & 25 day courses)	Phase 2	NIH RECOVER & Duke University	Completed
PROLIFIC	Paxlovid (15 day course)	Phase 2	Karolinska Institute	Completed
PaxLC	Paxlovid (15 day course)	Phase 2	Yale University	Completed, paper available
STOP-PASC	Paxlovid (15 day course)	Phase 2	Stanford University	Completed, paper available
outSMART-LC	AER002	Phase 2	UCSF	Completed
Evaluate the Efficacy and Safety of Ampligen	Ampligen	Phase 2	AIM ImmunoTech Inc.	Completed, results available
Phase 2 Study of RSLV-132	RSLV-132	Phase 2	Resolve Therapeutics	Completed, paper available
SARS-CoV-2 Specific Monoclonal Antibody for Long COVID	Sipavibart	Phase 2	Nova Southeastern University	Recruiting
PREVAIL-LC	Ensitrelvir	Phase 2	UCSF	Analysis in progress
AT1001 for the Treatment of Long COVID	Larazotide	Phase 2	Massachusetts General Hospital	Recruiting
Antiviral Clinical Trial for Long COVID	Truvada & Selzentry	Phase 2	CoRE at Mount Sinai	Recruiting
ERASE-LC	Remdesivir	Phase 4	University of Derby	Recruiting
ESSOR	LAU-7b	Phase 2 & 3	Laurent Pharmaceuticals Inc.	Completed

Table adapted and updated from Table 2 in Proal et al, 2025.

While researchers test existing COVID-19 treatments for Long COVID, biotech companies are working on the next iterations of those treatments. Invivyd, for example, is working on a next-generation monoclonal antibody called VYD2311 that should work better against more recent variants.

The company also aims to make its products easier to receive, as monoclonal antibodies currently require infusions at medical centers, which can be lengthy appointments. Future products might be available through injections into the muscle, as is common for vaccines, or even subcutaneous injections, which people could administer themselves at home, Elia said.

“We have a pretty good feeling that [monoclonal antibodies] for COVID tend to run safe and effective,” he said. “So the real question is, how long can we make them last, and how cheap, convenient, and easy can we make them to get?”

New antiviral research is also on the horizon. Japanese pharmaceutical company Shionogi has developed one such drug called ensitrelvir, which works similarly to Paxlovid but may have potential as a preventive option. UCSF researchers are conducting a clinical trial testing the drug as a Long COVID treatment, anticipating that the study will be completed by the end of 2025

according to its page on ClinicalTrials.gov.

And Pfizer is testing a next-generation antiviral called ibuzatrelvir, designed to improve on Paxlovid. While not under study for long COVID treatment, the company's phase 3 trial testing the drug's effectiveness will track whether study participants develop long COVID following SARS-CoV-2 infections.

Other current clinical trials, too, are repurposing antiviral treatments from different diseases to see if they help people with long COVID. For example, researchers at Massachusetts General Hospital are studying larazotide, a drug initially developed for celiac disease. The team reported this month in Science Translational Medicine that the drug helped alleviate symptoms of multisystem inflammatory syndrome in children (MIS-C) — and, notably, their trial matched health improvements with a decrease in spike protein levels.

The Massachusetts General Hospital researchers are still recruiting participants for a similar trial testing larazotide for children and adults with long COVID. Also currently recruiting: a trial at Mount Sinai's Cohen Center for Recovery from Complex Chronic Illnesses (CoRE) testing two HIV/AIDS drugs, Selzentry (maraviroc) and Truvada.

In parallel to these clinical trials, researchers continue to look for tests that could better track viral persistence and help trials "actually answer the questions that they set out to answer," as Peluso put it. UCSF has recently started a pilot of one new program, called VIPER, which will compare different potential persistence measurements, following the model of a similar program for HIV.

And more studies will tackle other long COVID hypotheses, too. Peluso described SARS-CoV-2 reservoirs as the "lowest-hanging fruit" in long COVID research: possible to test in trials with existing drugs, and also important to examine as they inform safety considerations for other types of studies. Now that some of the first-round studies are done, he said, researchers understand that, while viral persistence is likely a driver of symptoms in some people, it's far from the only one.

Speaking at the Keystone Symposia meeting in Santa Fe this week, he encouraged the long COVID field to be open-minded about this hypothesis. "We need to come to the middle," he said, between people who think "this must be the only mechanism that is important" and those who think it's not important at all. "What we need to do is actually figure this out, and we have not yet generated the data that we need to answer this question."

"We need to be going a lot farther down these various mechanistic pathways, and doing it a lot faster," he added later in his talk. "They all have therapeutics that we can name, and we need to be testing all of these pathways in parallel right now, not in series over decades."

Betsy Ladyzhets is a co-founder and the managing editor of The Sick Times.

This story is part of a series about promising long COVID treatment trials and how they are designed. To share tips or feedback for the series, reach out to us at editors@thesicktimes.org.

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