

What Do We Know About Paxlovid Rebound?

— And how should clinicians handle relapses after a 5-day course?

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It's not yet clear exactly how often it happens, but doctors are confident they're observing relapses after 5-day courses of nirmatrelvir/ritonavir (Paxlovid) for COVID-19.

Paul Sax, MD, clinical director of infectious diseases at Brigham and Women's Hospital in Boston, said most rebound cases he's seen have been mild, "but some, anecdotally, have been severe."

And even though COVID-19 has been associated with biphasic illness since the beginning of the pandemic, rebound with nirmatrelvir/ritonavir looks different, he said.

"I do think, though, that in these rebound cases, they have such a striking diminution in their symptoms, accompanied by clearance on home antigen tests, that at least part of the explanation for their biphasic illness must be nirmatrelvir acting as an antiviral," Sax told *MedPage Today*.

Despite widespread clinical observation, there have been less hard data on the phenomenon. Although it wasn't reported in the *New England Journal of Medicine* [publication](#) of nirmatrelvir/ritonavir data from the EPIC-HR trial, [data submitted by Pfizer to the FDA](#) (see pages 22-23) showed that "several subjects appeared to have a rebound in SARS-CoV-2 RNA levels around Day 10 or Day 14."

Pfizer also [told NBC News](#) that about 2% of participants in that trial experienced a rebound, compared with about 1.5% of those on placebo.

There's also a [preprint case report](#) from clinicians at the Boston VA involving a 71-year-old vaccinated and boosted patient who had a rapid and complete resolution of symptoms within two days of taking nirmatrelvir/ritonavir -- only to have a rebound a week later. Rebound symptoms were lesser, and resolved after two days, but the patient had clear peaks in viral load on day 1 and day 9, and no other respiratory pathogens were detected, Michael Charness, MD, and colleagues reported.

Fortunately, sequencing didn't reveal any treatment-emergent mutations, nor was there infection with a different subvariant, they reported. That's consistent with Pfizer data showing no evidence of resistance in rebound cases in preliminary analyses from EPIC-HR, according to the documents submitted to FDA.

But Sax warned that "we know in general with anti-infective treatments that are not completely effective at eradicating infection -- I'm thinking of our immunocompromised hosts -- there is potential to develop resistance, so that's something that will need to be carefully monitored."

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There are many plausible explanations as to why rebound can occur. Antiviral treatment may blunt a helpful immune response, Sax said. It could also be that some people may be prone to prolonged viral replication and thus destined to rebound after 5 days, and those ideas aren't mutually exclusive, he said. It's also unknown if rebound has anything to do with not completing the full course of therapy.

Better monitoring is needed, and fast, Sax said. Prospective observational trials can be organized relatively quickly, and large health systems like Geisinger, Kaiser, or the VA can examine their existing data. There may also be a need for randomized controlled trials to figure out how best to treat patients who relapse, he said.

In an email to *MedPage Today*, a Pfizer spokesperson said the company "continue[s] to monitor data from our ongoing clinical studies and post-authorization safety surveillance," but did not provide additional details on those assessments.

When asked about treatment duration, the Pfizer spokesperson said the 5-day course was "based on observations from the treatment of acute respiratory viral infections (e.g., [Xofluza] for influenza, remdesivir for hospitalized SARS-CoV-2, etc.) that showed a 5-day treatment duration to be adequate, with little evidence suggesting increased benefit of longer treatment durations."

"Based on these prior observations, the decision was made to evaluate a 5-day treatment course in EPIC-HR," the spokesperson stated, noting that results from the trial indicate the 5-day course was sufficient for the majority of patients. "There may be some patient populations who may benefit from longer durations of treatment, and we are considering additional studies to evaluate this in some populations."

In the meantime, clinicians are getting conflicting advice on how to proceed if a patient has a rebound. Pfizer CEO Albert Bourla [told Bloomberg](#) that patients who relapse can take another course of the antiviral.

The FDA, however, said earlier this week in a [statement from John Farley, MD, MPH](#), director of the Office of Infectious Diseases at the Center for Drug Evaluation and Research, that there's no evidence of benefit for repeating a treatment course in people who relapse.

Sax said he would limit re-treatment with a second course to the most immunocompromised and vulnerable patients, who are at the highest risk of hospitalization. For lower-risk patients with mild relapse:

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Patients who relapse and have symptoms and a positive antigen test need to behave as if they're contagious and can transmit the virus to others, he added.

Sax also said he's added a disclosure when he prescribes nirmatrelvir/ritonavir, telling patients they may experience a relapse after their treatment course.

"I prescribed Paxlovid this morning and part of my counseling now is that this can happen," he said. "I think it's important that clinicians remember to tell people this can happen."

[Kristina Fiore](#) leads MedPage's enterprise & investigative reporting team. She's been a medical journalist for more than a decade and her work has been recognized by Barlett & Steele, AHCJ, SABEW, and others. Send story tips to k.fiore@medpagetoday.com. Follow 
