Medical News & Perspectives

From Positive to Negative to Positive Again—The Mystery of Why COVID-19 Rebounds in Some Patients Who Take Paxlovid

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David Ho, MD, managed to avoid contracting COVID-19 for more than 2 years.

But SARS-CoV-2 finally got the best of the pioneering HIV researcher on an April trip to Paris for, of all things, a 2-day COVID-19 conference.

The irony is not lost on Ho, director of the Aaron Diamond AIDS Research Center at Columbia University. He figures he most likely became infected at a preconference dinner for a small group of attendees. They dined inside a restaurant, and the waitstaff weren't wearing masks, Ho explained in an interview.

Shortly after he returned home, Ho started coughing. His throat hurt, his head ached, his nose was runny, and he felt even more fatigued than a healthy person should after a quick trip across the pond and back. He immediately assumed that this was no cold, and a rapid antigen test followed by a polymerase chain reaction (PCR) test confirmed that he indeed had COVID-19.

About 12 hours after his symptoms arose, Ho swallowed his first dose of Pfizer's antiviral nirmatrelvir/ritonavir, better known as Paxlovid. By day 4, his symptoms had resolved and he tested negative for COVID-19. After testing negative again on day 5, he ended his isolation from his family but continued to test daily.

After 6 consecutive negative rapid antigen tests, plus a negative PCR test, Ho awoke feeling under the weather. "I tested myself immediately, and I was completely surprised that I was positive again," Ho recalled. "The initial shock was, 'Wow, this is positive. I've never seen this.'"

A PCR test confirmed the positive rapid antigen test, and it was "back to jail" for Ho. "If you're positive, you have to assume you're infectious to others," he explained.

In recent weeks, similar cases have been reported in the medical literature and on social media, prompting the Health Alert Network of the US Centers for Disease Control and Prevention (CDC) to issue a health advisory on May 24. COVID-19 rebound in people who've taken nirmatrelvir/ritonavir appears to be mild and short-lived, resolving, on average, in 3 days without additional anti-COVID-19 treatment, according to the advisory.

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"I would say the anecdotes are pretty consistent and pretty pronounced," H. Clifford Lane, MD, deputy director for clinical research and special projects at the National Institute of Allergy and Infectious Diseases, said in a recent interview. "Is there something here? If there is, what is it, and what do we do about it?"

No one is suggesting that people stop using the drug. In boldface type, the CDC's health advisory says the agency continues to recommend nirmatrelvir/ritonavir for early treatment of mild to moderate COVID-19 among people at high risk of progression to severe disease, the population eligible for the drug under its Emergency Use Authorization (EUA), granted by the US Food and Drug Administration (FDA) in December 2021.

However, the unexpected rebound phenomenon raises questions about how best to use this antiviral. "There are more questions than answers," Myron Cohen, MD, director of the University of North Carolina Institute for Global Health & Infectious Diseases in Chapel Hill and a leader of the National Institutes of Health's COVID-19 Prevention Network, noted in an interview.

Choices

Under its EUA, nirmatrelvir/ritonavir can be prescribed for mild to moderate COVID-19 in nonhospitalized patients aged 12 years or older who are at high risk of progression to severe disease due to age, obesity, cancer, or chronic diseases such as type 1 or type 2 diabetes. (High-risk patients who have mild to moderate COVID-19 but are hospitalized for other reasons are also eligible.)

A 3-pill dose of Paxlovid consists of 2 nirmatrelvir pills and 1 ritonavir pill, which has no activity against SARS-CoV-2 on its own. Nirmatrelvir is a protease inhibitor that blocks SARS-CoV-2 from replicating, while ritonavir boosts nirmatrelvir by slowing its metabolism in the liver. Ritonavir, which has been used to boost HIV protease inhibitors, also can slow the metabolism of an assortment of other drugs, increasing blood concentrations too much. In many cases, though, drug-drug interactions can be

managed by temporarily withholding, adjusting the dose of, or using an alternative to the concomitant medication and by increasing monitoring for potential adverse reactions, according to the National Institutes of Health's COVID-19 Treatment Guidelines, advice echoed in Infectious Diseases Society of America guidelines published May 6.

While the antiviral remdesivir (Veklury) also has been shown to be highly effective in decreasing the risk of hospitalization of people with mild to moderate COVID-19, patients must go to an infusion center on 3 consecutive days for treatment. Nirmatrelvir/ritonavir pills, on the other hand, can be picked up at the drugstore and taken at home.

Similarly, the antiviral molnupiravir (Lagevrio), which received an EUA in December 2021 for treating mild to moderate COVID-19 in high-risk adults aged 18 years or older, is taken as a pill for 5 days, starting within 5 days of symptom onset.

However, when compared with a placebo in the clinical trials supporting their EUAs, molnupiravir, a collaboration between Merck and Ridgeback Biotherapeutics, was not as effective as nirmatrelvir/ritonavir in keeping patients out of the hospital. Molnupiravir is authorized for use only by patients for whom alternative FDA-authorized COVID-19 treatments aren't accessible or clinically appropriate. Also, while nirmatrelvir/ritonavir is authorized for use in children as young as 12 years old, molnupiravir isn't authorized for use in children younger than 18 years because it may affect bone and cartilage growth. Molnupiravir, which stops SARS-CoV-2 from replicating but via a different pathway than nirmatrelvir/ritonavir, is not recommended for pregnant individuals because animal studies suggest it could cause fetal harm.

The US government has purchased 3.1 million courses of molnupiravir and 20 million courses of nirmatrelvir/ritonavir, to be delivered this year. The Office of the Assistant Secretary for Preparedness and Response, part of the US Department of Health and Human Services, maintains a web-based site locator for drugstores and other facilities that have received an order of nirmatrelvir/ritonavir or molnupiravir in the previous 2 months or reported their availability within the previous 2 weeks. In addition, a constantly updated website enables people to search specifically for SARS-CoV-2 treatments in their community.

Although nirmatrelvir/ritonavir protects against severe COVID-19 in symptomatic people who've tested positive for SARS-CoV-2 infection, it doesn't prevent individuals from becoming positive and symptomatic, according to an April 29 Pfizer press release about the findings of a randomized, placebo-controlled clinical trial among adults who had been exposed to SARS-CoV-2 through a household contact.

A Different World

Rebound isn't even mentioned in the article that in April reported results from the EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) trial, which was the basis of Paxlovid's EUA. Omicron isn't mentioned either because trial participants, none of whom were vaccinated, contracted COVID-19 before Omicron burst onto the scene.

A clinical trial among unvaccinated people that predates Omicron, which now accounts for 100% of circulating SARS-CoV-2 in the US, "holds little clinical relevance" today, Emory University School of Medicine and Grady Health System infectious disease specialist Carlos del Rio, MD, said in an interview. Even unvaccinated people today are different from unvaccinated people pre-Omicron because they're more likely to have had at least 1 previous COVID-19 infection, Cohen pointed out.

A study posted online May 26 but not peer-reviewed is one of the first to explore real-world effectiveness of nirmatrelvir/ritonavir and molnupiravir in vaccinated as well as unvaccinated patients infected with Omicron, according to its authors.

Conducted in Hong Kong, the retrospective cohort study focused on nearly 1.1 million nonhospitalized patients territory wide with confirmed SARS-CoV-2 infection during the Omicron BA.2.2 wave between February 26 and May 3, 2022. Among them, 5257 took molnupiravir and 5663 took nirmatrelvir/ritonavir.

Both antivirals were associated with lower all-cause mortality risk—a 39% reduction for molnupiravir, 75% for nirmatrelvir/ritonavir—compared with no antiviral use. Both also were associated with a lower risk of in-hospital disease progression—36% for molnupiravir and 53% for nirmatrelvir/ritonavir—compared with no antiviral use. Nirmatrelvir/ritonavir was associated with a 31% lower risk of hospitalization, while the hospitalization risk in patients who took molnupiravir was comparable with that of patients who didn't take an antiviral.

Neither drug was associated with as high a level of protection among the Hong Kong patients infected with Omicron as was seen in its clinical trial among unvaccinated patients infected by the Delta variant. (In its trial, molnupiravir reduced hospitalization risk by 30% compared with placebo, while nirmatrelvir/ritonavir reduced it by 88%.)

In the Hong Kong study, nirmatrelvir/ritonavir use was associated with greater and more consistent protection than molnupiravir use, and the protective effects of nirmatrelvir/ritonavir were similar regardless of vaccination status and age. However, the apparent superiority of nirmatrelvir/ritonavir to molnupiravir in the study could have been due in part to a higher proportion of patients older than 65 years and a lower proportion of fully vaccinated patients among those who received the latter drug, the authors noted.

Pfizer is currently enrolling an estimated 1980 adults in a trial comparing Paxlovid with placebo, similar to EPIC-HR. But in the newer trial, participants have only a standard risk, not a high risk, of progressing from mild or moderate COVID-19 to severe disease. Another major difference between EPIC-HR and EPIC-SR (standard risk) is that all the participants are likely to have been infected with Omicron, not Delta, given the timing of the trial. Anyone who received any COVID-19 vaccine within 12 months of screening is ineligible to enroll in EPIC-SR, which means participants could have received their primary vaccine doses but not boosters.

Is It the Drug, or Is It the Disease?

The CDC's May 24 health advisory noted that "a brief return of symptoms may be part of the natural history of SARS-CoV-2…infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status."

The FDA is aware of cases in which patients treated with Paxlovid tested positive at least once after testing negative, John Farley, MD, MPH, director of the Office of Infectious Diseases at the FDA's Center for Drug Evaluation and Research, noted in an early May update for health care professionals. An additional analysis of the EPIC-HR clinical trial data showed that about 1% to 2% of participants in both the treatment and placebo groups tested positive after testing

negative, Farley wrote, "so it is unclear at this point that this is related to drug treatment."

In an email, Pfizer spokeswoman Jerica Pitts echoed the CDC and FDA. "We believe the return of elevated detected nasal viral RNA [is] uncommon and not uniquely associated with treatment," she wrote.

Ho, coauthor of a study posted May 23 about 10 people—he is the second case described in the report—who rebounded after taking nirmatrelvir/ritonavir, disagrees. When asked whether he thought the rebound could be part of the natural course of SARS-CoV-2 infection, he replied "absolutely not."

As evidence, he and his coauthors pointed to the experience of the National Basketball Association (NBA), which tests personnel daily. From December 14, 2021, to March 1, 2022, a period during which Omicron was dominant, rebounds occurred only on the basketball court—not among the nearly 1000 NBA personnel who were diagnosed with COVID-19 but not treated with nirmatrelvir/ritonavir, according to Ho and his coauthors. Their study had not undergone peer review.

However, Johns Hopkins breast cancer specialist Tatiana Prowell, MD, recently tweeted that she's heard from physicians who've had patients with COVID-19 rebound or test positive on rapid antigen tests for up to 3 weeks, even though they never took nirmatrelvir/ritonavir or any other treatment. Perhaps, she speculated, Omicron and its subvariants take longer to peak or to clear than earlier SARS-CoV-2 variants. (Prowell had recently tweeted about how a household member's symptoms disappeared and rapid antigen test results turned negative after completion of a course of nirmatrelvir/ritonavir. A week later, though, the symptoms returned, as did positive rapid antigen test results.)

Still, "[y]ou just didn't hear about many rebounds pre-Paxlovid," Robert Wachter, MD, who tweeted in May about wife Katie Hafner's rebound after taking Paxlovid, said in an interview. "You have to say that there's something about Paxlovid and Omicron that predisposes you to this phenomenon."

The fact that few EPIC-HR participants experienced a rebound "gives me less confidence in all of the findings," said Wachter, chair of the University of California, San Francisco, Department of Medicine. If he tested positive—despite his wife's COVID-19 bout, he hasn't—Wachter said he'd be "much more on the borderline" trying to decide whether to take Paxlovid than he would have been before he started hearing about rebounds.

"Even if rebounds turn out to be mild and self-limited, they have consequences for people in terms of their ability to go back to work or to school," Wachter pointed out.

No one yet knows how common rebound is among people who've taken Paxlovid. "You need some very objective evaluation of it," Lane said.

Ho dismisses Pfizer's contention that rebound is uncommon. He and his coauthors noted that 5 of the 10 relapses described in their report occurred within 2 families—2 in his family and 3 in another—suggesting it isn't rare.

That's concerning, Ho said, because it appears that people who experience a relapse can infect others. Among the 10 cases in the report he coauthored, viral load during the relapse was comparable to levels during the initial infection. During their relapse, 1 symptomatic and 1 presymptomatic patient transmitted SARS-CoV-2 to family members, Ho and his coauthors wrote.

Trying to Figure It Out

Ho likely is one of very few people who've relapsed after taking nirmatrelvir/ritonavir and then sequenced their own virus both the first and second time around. (At least 1 other leading virologist, Peter Hotez, MD, PhD, of the Baylor College of Medicine, has revealed that he also experienced a post-Paxlovid relapse.)

Both of Ho's sequences were identical, ruling out a couple of possible explanations for his relapse, he said. It couldn't have been due to a stroke of bad luck—a second SARS-CoV-2 infection just as he was getting over his first one. And it couldn't have resulted from the virus becoming resistant to nirmatrelvir. If either were the case, the virus pair wouldn't have been identical.

Scientists have proposed a few other possible explanations for rebounds after nirmatrelvir/ritonavir treatment. "Question number 1 in my mind is the timing. I think maybe we're giving it too early," del Rio said. Perhaps, Wachter speculated, "If you get started right away, maybe you suppress the virus [and] the immune system doesn't rev up in the way it normally would." He and others have also suggested that 5 days might not be a long enough treatment course. "All these theories are total handwaving," Wachter acknowledged.

To answer the outstanding questions about relapses, "I'm not sure we need a clinical trial in the classical definition," del Rio said. "We need post-approval data." It's being collected, he said, but the findings probably won't be available for months. For now, there is no evidence that additional treatment with nirmatrelvir/ritonavir is needed when a rebound is suspected after a 5-day course, according to both the CDC's advisory and FDA official Farley's recent update.

Despite all the questions about the rebound phenomenon, "the biggest challenge we're having with the drug is it's not being used as frequently as it should," del Rio said. "Primary care physicians are freaked out about the drug-drug interactions." The people in whom COVID-19 is most likely to progress to a serious or even deadly infection are also the ones most likely to be taking multiple medications, he noted.

One thing is for sure, testing is more important than ever, given the availability of effective treatments for COVID-19, Cohen said. "I see a sea change in the management of respiratory infections."

Nobody says, "Oh, I think I have a cold" anymore, he explained. "If we're going to treat people with COVID, we need to know if they have COVID." ■

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