

# Rapid Relapse of Symptomatic SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir

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## Case Report

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# Abstract

Initiation of NM/R treatment on Day 0 in a 71-year-old vaccinated and boosted male resulted in rapid resolution of COVID-19 symptoms followed one week later by the development of typical cold symptoms. SARS-CoV-2 viral load fluctuated in parallel with symptoms, with two distinct peaks on Day 1 and Day 9 of illness. No other respiratory pathogens were identified. Viral samples demonstrated sequence identity for the omicron subvariant BA.1 on Days 1, 7, and 11. Our findings suggest that viral replication and COVID-19 symptoms may recur after very early treatment with NM/R before natural immunity is sufficient to fully clear SARS-CoV-2.

## Background

Nirmatrelvir is a SARS-CoV-2 main protease inhibitor that blocks replication of SARS-CoV-2 and markedly reduces disease severity in unvaccinated individuals at risk for progression of COVID-19 (1). Treatment with nirmatrelvir combined with ritonavir (NM/R) an average of 2.9 days after symptom onset induced a rapid and progressive reduction in SARS-CoV-2 viral load (1). Here we describe a surprising rebound of viral load and symptoms 4 days after the completion of early NM/R treatment.

### Objective

Primary care providers manage mild COVID-19 in patients who are at risk for progression to severe illness. This case report highlights the potential for recurrent, symptomatic SARS-CoV-2 replication after successful early treatment with NM/R.

## Case Report

A 71-year-old, fully vaccinated and boosted male with intermittent asthma had a high-risk exposure on Day -2. Nasal quantitative reverse-transcriptase polymerase chain reaction (RT-PCR) was negative on the morning of Day -1, but mild rhinorrhea developed that evening, and antigen testing (BinaxNow, Abbott) was positive the morning of Day 0. Symptoms progressed rapidly on Day 0 to sore throat and increasing rhinorrhea, coryza, asthma, cough, fatigue, malaise, chills, and fever of 38.4°C. Oral NM/R was started at 3 PM on Day 0 and continued every 12 hours through the morning of Day 5. Symptoms improved rapidly after the start of NM/R, with only mild rhinorrhea and asthma on Day 1 and complete resolution of symptoms by Day 2. On Day 9, while still isolating, he developed typical cold symptoms with rhinorrhea, sore throat, coryza, and asthma; these peaked on Day 10 and resolved by Day 12.

RT-PCR cycle threshold and antigen testing fluctuated in parallel with symptoms, and there were two distinct peaks of viral load and symptoms on Day 1 and Day 9 (Figure). Respiratory pathogen screen (Biofire RP2.1) on Day 10 was positive for SARS-CoV-2 and negative for 21 other respiratory pathogens. Viral genome sequencing (Ion Torrent Genexus Integrated Sequencer, ThermoFisher Scientific) demonstrated sequence identity for the omicron subvariant BA.1 on Days 1, 7, and 11. Serum anti-spike IgG was positive (>25,000 absolute units per ml) on Day 13, and anti-nucleocapsid IgG was 0.51 on Day

14 and 1.93 on Day 21 (considered positive when index is >1.4). Antigen testing remained negative on Day 35.

## Discussion

Clinicians should note the potential for a rapid relapse of COVID-19 symptoms following the completion of early, effective treatment with NM/R. Treatment with NM/R was started on the first full day of symptoms, just one day after a negative PCR. The resumption of SARS-CoV-2 replication after the completion of NM/R treatment may have triggered the delayed onset of cold symptoms, which are thought to be immune mediated (2). No other respiratory viruses were identified at the peak of cold symptoms, and vaccine and developing natural immunity may have minimized symptom severity and duration. Sequencing indicated that this relapse was not due to a treatment-emergent mutation or infection with a different subvariant. Antigen testing closely paralleled PCR results, as described (3), and might prove helpful in the initial evaluation of recurrent COVID-19 symptoms following NM/R treatment.

Vaccination and boosters provide only modest protection against symptomatic infection with the omicron variant (4); hence, the development of natural immunity to unique omicron epitopes may be necessary to clear omicron virus, even in vaccinated persons. Natural immunity to SARS-CoV-2 infection arises over several weeks (5) and is likely better developed when NM/R treatment ends on day 10 than Day 5. These findings suggest that very early treatment with NM/R may transiently suppress viral replication before natural immunity is sufficient to complete the clearance of SARS-CoV-2. The FDA analysis of submitted data on NM/R indicated rebound increases in SARS-CoV-2 viral load in several subjects between Day 10 and Day 14, but no clinical details were described (6). In contrast, RT-PCR cycle thresholds above 30 were not detected between Day 11 and Day 15 in NBA team employees and players with the SARS-CoV-2 omicron variant who were diagnosed during frequent surveillance and did not receive NM/R (7).

This report is limited by the availability of just one, comprehensively studied case. Further work is required to determine the frequency, duration, and spectrum of rebound symptoms and whether late recrudescence of viral replication is associated with a heightened risk of transmission. Because this is a single case, it is not possible to know whether rebound occurs more frequently during treatment with NM/R than in untreated patients. The potential for symptomatic rebound of viral load, with or without antiviral treatment, has important implications for clinical management and infection prevention.

## Declarations

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This work was supported by the VA Boston Healthcare System. Dr. Charness has equity in Pfizer, the maker of nirmatrelvir/ritonavir. Dr. Gupta reports past or current equity in Pfizer, Abbott, and Moderna. She

is a co-investigator on a grant to the institution from Pfizer on an unrelated topic. The remaining authors have no conflicts of interest to disclose.

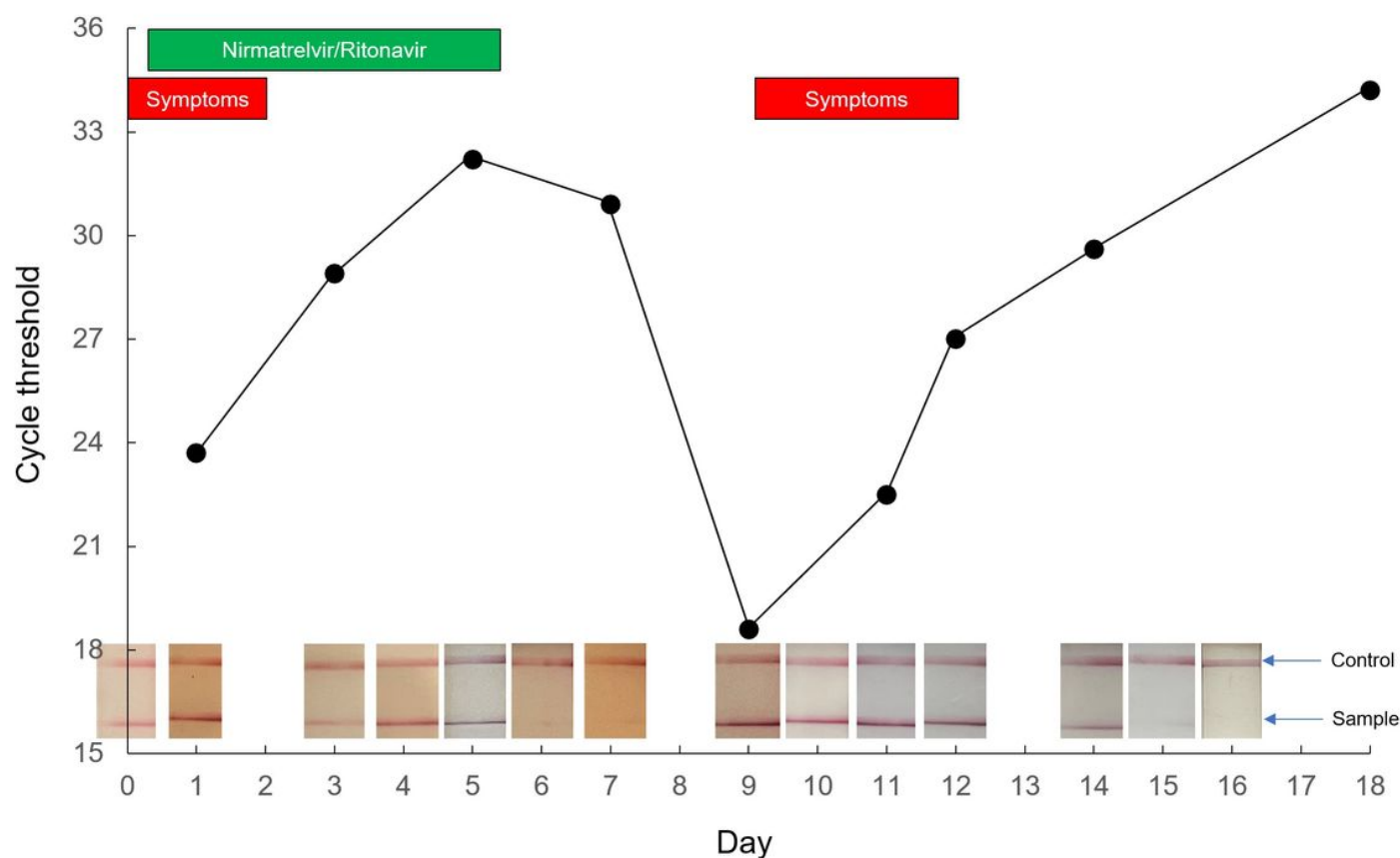
The IRB determined this was quality improvement work not requiring further review.

The patient consented to participate and publish their clinical data and images in the case report.

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## Figures



**Figure 1**

Time course of SARS-CoV-2 infection and COVID-19 symptoms. Day 0 was the first day of positive testing and the first full day of symptoms. Antigen tests are displayed next to the X-axis, and the data points represent cycle threshold determined by nasal mid-turbinate PCR. The timing of symptoms and treatment with nirmatrelvir/ritonavir is indicated with red and green rectangles, respectively. Cycle threshold is inversely proportional to viral load. All PCR samples were run on the Roche Cobas platform except for Day 12, which was run on the Cepheid platform.