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Symptom and Viral Rebound in Untreated SARS-CoV-2 Infection

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Background: Although symptom and viral rebound have been reported after nirmatrelvir-ritonavir treatment, the trajectories of symptoms and viral load during the natural course of COVID-19 have not been well described.

Objective: To characterize symptom and viral rebound in untreated outpatients with mild to moderate COVID-19.

Design: Retrospective analysis of participants in a randomized, placebo-controlled trial. (ClinicalTrials.gov: NCT04518410)

Setting: Multicenter trial.

Patients: 563 participants receiving placebo in the ACTIV-2/A5401 (Adaptive Platform Treatment Trial for Outpatients With COVID-19) platform trial.

Measurements: Participants recorded the severity of 13 symptoms daily between days 0 and 28. Nasal swabs were collected for SARS-CoV-2 RNA testing on days 0 to 14, 21, and 28. Symptom rebound was defined as a 4-point increase in total symptom score after improvement any time after study entry. Viral rebound was defined as an increase of at least 0.5 log₁₀ RNA copies/mL from the immediately preceding time point to a viral load of 3.0 log₁₀ copies/mL or higher. High-level viral rebound was defined as an increase of at least 0.5 log₁₀ RNA copies/mL to a viral load of 5.0 log₁₀ copies/mL or higher.

Results: Symptom rebound was identified in 26% of participants at a median of 11 days after initial symptom onset. Viral rebound was detected in 31% and high-level viral rebound in 13% of participants. Most symptom and viral rebound events were transient, because 89% of symptom rebound and 95% of viral rebound events occurred at only a single time point before improving. The combination of symptom and high-level viral rebound was observed in 3% of participants.

Limitation: A largely unvaccinated population infected with pre-Omicron variants was evaluated.

Conclusion: Symptom or viral relapse in the absence of antiviral treatment is common, but the combination of symptom and viral rebound is rare.

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Nirmatrelvir-ritonavir (Paxlovid [Pfizer]) is a recommended treatment for outpatients with mild to moderate COVID-19 and risk factors for severe disease (1). Widespread use of nirmatrelvir has been accompanied by reports of worsening symptoms (2) and virologic rebound (3–5) after treatment completion. Of note, clinical relapse has also been described in patients who did not receive nirmatrelvir therapy (6, 7), but rigorous studies that can define the frequencies of symptom and viral rebound during the natural course of COVID-19 are lacking. Understanding these frequencies in the absence of treatment is important to understanding the role that antiviral therapy may play in these observations. To date, much of the reported literature is observational, is focused on only symptoms or only virology, or is limited by the lack of systematically collected samples and data in a rigorously controlled setting. Even in the phase 3 clinical trial of nirmatrelvir-ritonavir in higher-risk outpatients with mild to moderate COVID-19 (EPIC-HR [Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients]), the frequency of viral rebound was likely underestimated

because viral RNA was quantified at only 2 postintervention time points and symptom rebound was not described (8).

In this study, we evaluated the incidence of both symptom and viral rebound in untreated outpatients with mild to moderate COVID-19 who received a placebo in the ACTIV-2/A5401 (Adaptive Platform Treatment Trial for Outpatients With COVID-19) multicenter, phase 2/3, platform, randomized trial by the AIDS Clinical Trials Group. A strength of this study was that participants collected daily anterior nasal (AN) swabs for the first 2 weeks (in the phase 2 studies) for quantitative viral load testing and completed daily symptom diaries for the first 29 days (in the phase 2 and 3 studies). This intensive sampling in the framework of a rigorous randomized, placebo-controlled trial allowed for robust assessment of the frequencies of symptom and viral rebound in untreated persons.

METHODS

Overview of Study Participants

Adults (aged ≥18 years) with documented acute SARS-CoV-2 infection were enrolled within 7 to 10 days (initially 10, then decreased to 7 days) of COVID-19 symptom onset in the ACTIV-2/A5401 platform trial of COVID-19 therapeutics for outpatients with mild to moderate COVID-19 (NCT04518410). Viral rebound analysis was restricted to participants who enrolled between November

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2020 and July 2021 in the placebo groups of the following ACTIV-2/A5401 phase 2 studies: bamlanivimab, 7000 mg ($n = 46$); bamlanivimab, 700 mg ($n = 112$); and amubarvimab plus romlusevimab ($n = 109$) monoclonal antibodies (Supplement Figure 1, available at Annals.org). For the symptom rebound analysis, an additional 296 participants were included from the placebo group of the phase 3 trial of amubarvimab plus romlusevimab monoclonal antibodies. The bamlanivimab studies enrolled participants who were at standard and higher risk for progression to severe COVID-19, whereas the amubarvimab plus romlusevimab studies enrolled only high-risk participants. All participants in the phase 2 studies were enrolled in the United States, whereas those in the amubarvimab plus romlusevimab phase 3 evaluation were enrolled in the United States, Argentina, Mexico, South Africa, and Brazil. The protocol was approved by a central institutional review board, Advarra (Pro00045266), for U.S. sites (with additional local institutional review board review and approval as required by the site) and by local ethics committees for sites outside the United States. All participants provided written informed consent before undergoing study procedures.

Study Assessments

Participants completed a daily symptom diary from study day 0 (day of study entry) through day 28, where they recorded the severity of 13 targeted symptoms. These symptoms were feverishness, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain or aches, fatigue, headache, chills, nasal obstruction or congestion, nasal discharge, nausea, vomiting, and diarrhea. Each symptom was self-assessed and scored daily by the participant as absent (0 points), mild (1

point), moderate (2 points), or severe (3 points). Total symptom score was calculated on each day as the sum of scores for the 13 targeted symptoms (possible range, 0 to 39) (9, 10). Daily AN swabs were obtained from study entry (day 0) through study day 14 and at day 28. For bamlanivimab participants, an additional sample at day 21 was collected. Levels of SARS-CoV-2 RNA were quantified from AN swab samples, as previously described (11-13).

Statistical Analysis

Symptom rebound after initial improvement was identified when the highest symptom score after day 0 was at least 4 points higher than the lowest score up to that study day. The magnitude of the difference is the difference in total symptom scores between those 2 time points. Participants who were hospitalized were assigned the highest possible symptom score of 39 during the days they were hospitalized because symptom score data were frequently unavailable during these time intervals (diaries were not required to be completed during hospitalization). Missing data were ignored in the calculation of symptom rebound because only 4% of individual symptom scores were missing across the 13 symptoms and 29 days of the diary, and none of the participants with symptom rebound had missing data on the days used in calculating the extent of symptom rebound. We evaluated symptom rebound after initial improvement using the primary analysis definition in the following steps: 1) identified the minimum and maximum total symptom scores (minimum score identified between day 0 and the maximum score), and presence of a symptom score decline between day 0 and the minimum score, 2) calculated the difference between

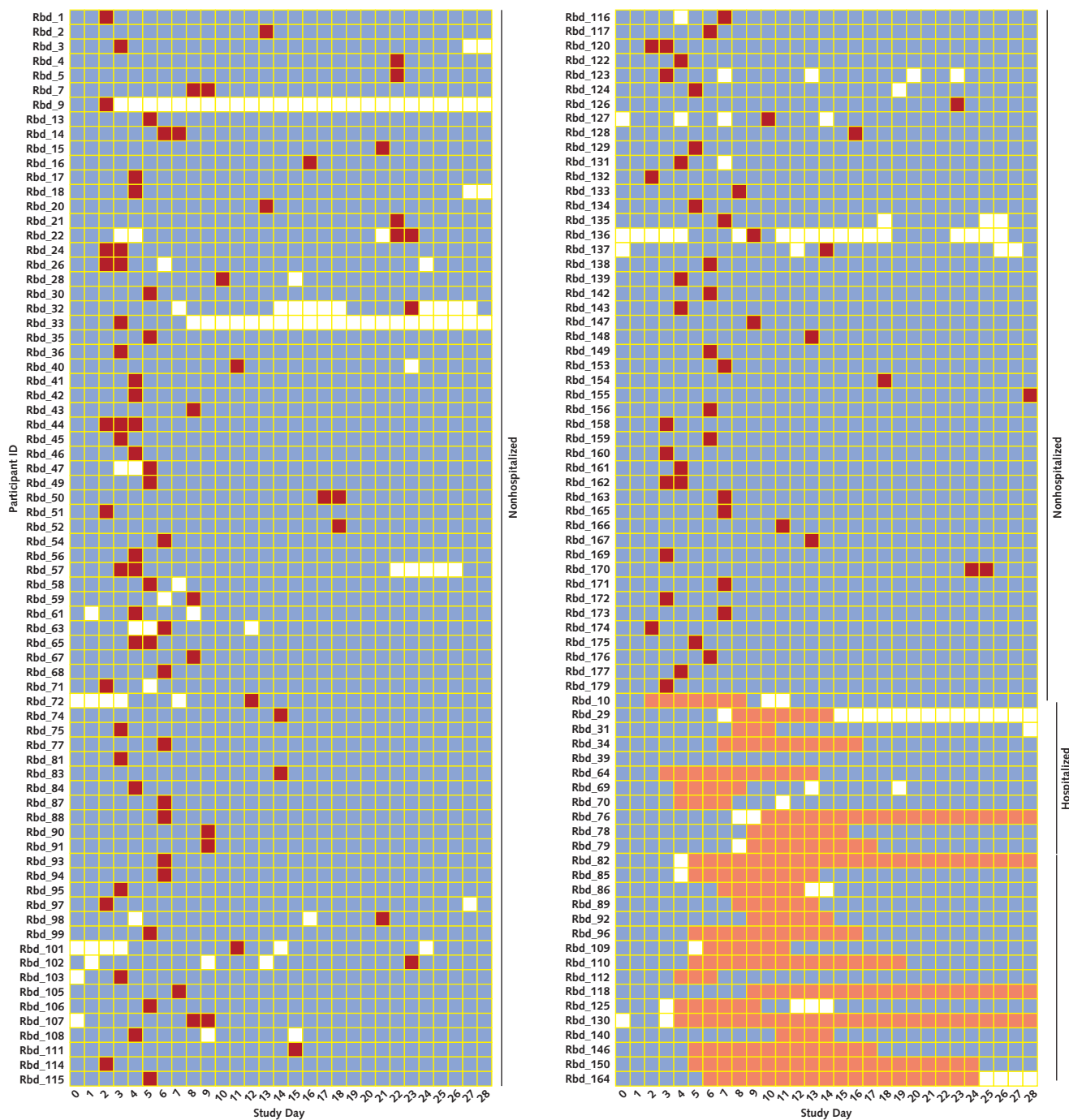
Table 1. Demographic Characteristics of Participants Categorized as Rebounders and Nonrebounders After Study Enrollment (Primary Analysis Definition)*

Characteristic	Symptom Rebound Analysis ($n = 563$)				Nasal Viral Rebound Analysis ($n = 261$)			
	All ($n = 563$)	Rebounders ($n = 148$)	Nonrebounders ($n = 415$)	Odds Ratio (95% CI) Comparing Rebounders vs. Nonrebounders	All ($n = 261$)	Rebounders ($n = 82$)	Nonrebounders ($n = 179$)	Odds Ratio (95% CI) Comparing Rebounders vs. Nonrebounders
Median age (Q1, Q3), y	49 (38, 57)	50 (39, 59)	48 (37, 57)	1.07 (0.94-1.23)†	48 (36, 56)	51 (38, 60)	47 (36, 55)	1.14 (0.95-1.38)†
Female sex, %	51	59	48	1.53 (1.05-2.25)	49	46	50	0.85 (0.50-1.44)
Race/ethnicity, %								
White	77	74	78	0.82 (0.53-1.27)	81	84	80	1.45 (0.73-3.06)
Non-White	23	26	22	1.23 (0.79-1.89)	19	16	20	0.69 (0.33-1.38)
Higher risk, %	81	88	78	2.00 (1.18-3.55)	65	56	69	0.57 (0.33-0.97)
Median days from symptom onset to enrollment (Q1, Q3)	6 (4, 7)	5 (3, 7)	6 (4, 7)	0.92 (0.84-0.99)	6 (4, 8)	6 (4, 7)	6 (4, 8)	0.91 (0.81-1.02)
Symptom score at enrollment (study day 0) (Q1, Q3)	10 (6, 14)	13 (8, 18)	9 (5, 13)	1.08 (1.05-1.12)	9 (6, 13)	9 (6, 13)	9 (6, 13)	0.98 (0.93-1.03)
Median AN SARS-CoV-2 viral load at enrollment (Q1, Q3), \log_{10} copies/mL	4.06 (2.0, 6.02)	5.05 (2.00, 6.82)	3.85 (2.00, 5.74)	1.17 (1.06-1.28)	4.31 (2.13, 6.14)	5.36 (3.82, 6.90)	3.50 (2.00, 5.76)	1.40 (1.22-1.60)

AN = anterior nasal; Q = quartile.

* Symptom rebound was defined as a 4-point increase in total symptom score after improvement any time after study enrollment, whereas viral rebound was defined as an increase of 0.5 \log_{10} RNA copies/mL from the prior time point. Statistical analysis was done using logistic regression comparing rebounders versus nonrebounders. Significant odds ratio values are shown in bold.

† Indicates odds ratio of age per 10 y between rebounders and nonrebounders.

Figure 1. Heat map of symptom score rebound after study enrollment (primary analysis definition).

The heat map shows participants with symptom rebound (≥ 4 -point increase in symptom score) after initial symptom improvement after study enrollment. Individual participants are shown in rows, and study days are shown in columns. Red squares represent days meeting symptom rebound criteria, orange squares days of hospitalization, blue squares days that did not meet symptom rebound criteria, and gray squares days on which study diaries were not collected. ID = identification number.

maximum and minimum scores, and 3) classified symptom rebound when a symptom score was at least 4 points higher than the minimum score (Supplement Figure 2, available at [Annals.org](https://annals.org)). Participants who were hospitalized were manually checked for symptom score rebound.

Participants were included in viral rebound analyses if SARS-CoV-2 RNA levels were available from at least 3 time points (the median number of measurements per participant was 16 [1st quartile {Q1}, 14 measurements; 3rd quartile {Q3}, 16 measurements]). Viral rebound was

defined as an increase of at least 0.5 log₁₀ RNA copies/mL from the immediately preceding time point after an initial documented decrease in viral RNA level any time after day 0 (primary analysis definition). The rebounding RNA level must meet a minimum threshold of 3.0 log₁₀ copies/mL (Supplement Figure 3, available at Annals.org). Sensitivity analyses considered the frequency of viral rebound meeting minimum thresholds of at least 4.0, 5.0, and 6.0 log₁₀ RNA copies/mL. The threshold of 3.0 log₁₀ copies/mL was similar to that used in the analysis of viral rebound in EPIC-HR (8), whereas the threshold of 5.0 log₁₀ copies/mL was chosen on the basis of our previous studies that showed a high rate of viral culture positivity at 5.0 log₁₀ copies/mL or higher (14), which may have transmission implications. Levels of SARS-CoV-2 RNA below the lower limit of quantification were imputed as 2.0 log₁₀ copies/mL.

To mirror the timing of a 5-day course of nirmatrelvir-ritonavir, an additional secondary analysis was done that restricted symptom and viral RNA measures before day 5. In this analysis, participants were classified as rebounders only if their rebound occurred on or after day 5.

Continuous variables are presented as medians with IQRs, and categorical variables are expressed as frequencies or percentages. Predictors of symptom and viral rebound were evaluated using logistic regression and summarized with odds ratios with 95% CIs. All statistical analyses were done in GraphPad Prism, version 9.1.1 (GraphPad Software).

Role of the Funding Source

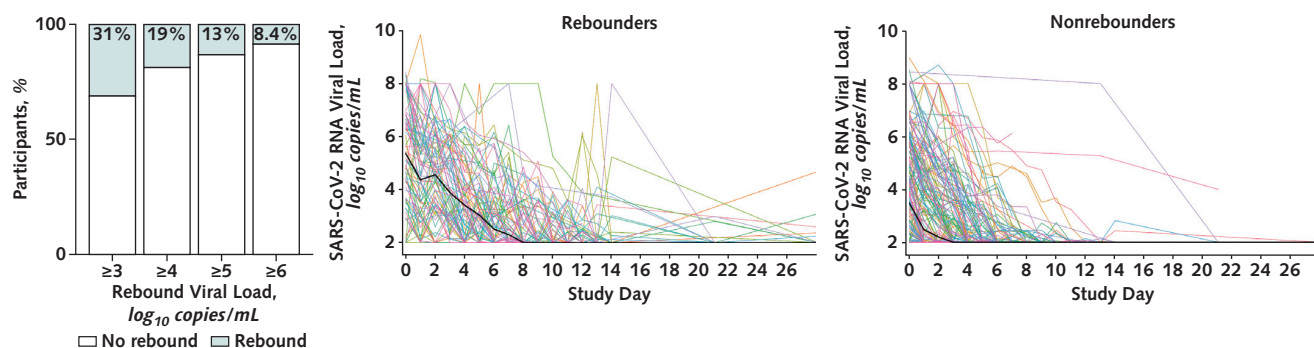
The study sponsor, the National Institutes of Health Division of AIDS, participated in the design of the study and reviewed and approved the protocol before study initiation. Oversight and responsibility for data collection were delegated by the sponsor to PPD clinical research, a contract research organization.

RESULTS

We first assessed the frequency of symptom rebound (≥ 4 -point increase in total symptom score) after initial improvement in 563 participants who received placebo in the ACTIV-2 trial (Table 1). The median age was 49 years, 51% of participants were female, 81% were categorized as having high risk for severe COVID-19, and participants enrolled at a median of 6 days (Q1, 4 days; Q3, 7 days) after symptom onset. We found that symptom rebound occurred in 26% ($n = 148$) of participants at a median of 6 days (Q1, 4 days; Q3, 9 days) after study enrollment and 11 days (Q1, 9 days; Q3, 14 days) after initial symptom onset (Figure 1); 5% ($n = 27$) of participants were considered to have symptom rebound due to hospitalization. Symptom rebound in nonhospitalized participants was short, lasting 1 day in 89% of those experiencing it (range, 1 to 3 days). Patients with symptom rebound were more likely to be female and have higher risk for severe disease, shorter time since symptom onset, higher total symptom score at day 0, and higher nasal viral RNA level at study enrollment (Table 1). There were no significant differences between symptom rebounders and nonrebounders in age or race/ethnicity. In the secondary analysis that evaluated symptom rebound on or after study day 5 (to simulate a time period after nirmatrelvir), 22% ($n = 121$) of participants met criteria for symptom rebound, occurring a median of 9 days after study enrollment and 14 days after initial symptom onset (Supplement Table 1 and Supplement Figure 4, available at Annals.org); 3% ($n = 15$) were considered to have symptom rebound due to hospitalization.

The viral rebound analysis included 261 participants (Table 1), of whom 31% ($n = 82$) had viral rebound to 3.0 log₁₀ copies/mL or higher after study entry. In addition, 19%, 13%, and 8.4% of the participants had viral rebound with rebounding RNA levels reaching at least 4.0, 5.0, and 6.0 log₁₀ copies/mL, respectively (Figure 2). Most viral rebound was transient, because 95% of viral rebound events occurred at only a single time point before the viral

Figure 2. Description of AN SARS-CoV-2 RNA rebound after study enrollment (primary analysis definition).



AN = anterior nasal. Left. Bar graph shows percentage of participants having AN SARS-CoV-2 RNA rebound ≥ 0.5 log₁₀ copies/mL at any follow-up time point after study enrollment. The frequencies of viral rebound were assessed with a minimum rebound viral load of ≥ 3.0 , ≥ 4.0 , ≥ 5.0 , or ≥ 6.0 log₁₀ RNA copies/mL. Center and right. These graphs show AN SARS-CoV-2 RNA in log₁₀ copies/mL by study day in rebounders and nonrebounders, respectively. The thick black lines show median AN SARS-CoV-2 RNA copies/mL for each day. The y-axes show AN SARS-CoV-2 RNA in log₁₀ copies/mL, whereas the x-axes denote study day.

Table 2. Frequency of Participants Meeting Both Symptom and Viral Rebound Criteria After Study Enrollment (Primary Analysis Definition)

Category	Symptom Rebound After Improvement
Low-level viral (≥ 3.0 and < 5.0 \log_{10} RNA copies/mL) and symptom score (≥ 4 points) rebound, <i>n</i> (%)	8 (3.1)
High-level viral (≥ 5.0 \log_{10} RNA copies/mL) and symptom score (≥ 4 points) rebound, <i>n</i> (%)	7 (2.7)

RNA load decreased. Participants with viral RNA rebound were less likely to be at higher risk for severe disease, and had higher median AN levels of viral RNA at study entry (Table 1). There were no significant differences in sex, race/ethnicity, time since symptom onset, or day 0 total symptom score between those with and without viral rebound. In the secondary analysis of viral loads on or after study day 5, viral rebound was identified in 20% (*n* = 53) of participants. In this analysis, 11%, 6.5%, and 3.8% of participants had viral rebound with a viral load reaching at least 4.0, 5.0, and 6.0 \log_{10} RNA copies/mL, respectively (Supplement Figure 5, available at [Annals.org](#)).

Finally, we assessed the frequency with which participants met criteria for both symptom and viral rebound. This analysis was restricted to participants with measurements of both daily nasal SARS-CoV-2 RNA and symptom score (*n* = 261). Although symptom and viral rebound were each commonly seen, the combination was rare. Only 3.1% of participants had both symptom and viral rebound (rebound viral RNA reaching between 3.0 and 5.0 \log_{10} copies/mL), and only 2.7% had both symptom and high-level viral rebound (rebound viral RNA reaching 5.0 \log_{10} copies/mL or higher) (Table 2). When rebound occurring on or after study day 5 was assessed (to simulate a time period after nirmatrelvir), only 1.2% of participants met criteria for both symptom and high-level viral rebound (Supplement Table 2, available at [Annals.org](#)).

DISCUSSION

Isolated cases of symptom and viral rebound and recurrence of culture-positive virus have been reported after nirmatrelvir-ritonavir treatment (3–5, 15). However, much of the literature has described the co-occurrence of symptom and viral rebound in noncontrolled settings or with limited sampling. To help improve the understanding of the natural course of COVID-19, we analyzed the symptom and viral rebound dynamics of participants receiving placebo in the randomized, placebo-controlled ACTIV-2/A5401 trial for outpatients. Overall, we found that viral or symptom rebound after initial improvement was relatively common, with 1 in 4 participants having symptom rebound and almost 1 in 3 having viral rebound during their infection, as assessed by daily symptom and nasal virus sampling. However, both symptom and viral rebound were short, lasting only 1 day in most participants. In addition, the combination of symptom and high-level

viral (≥ 5.0 \log_{10} RNA copies/mL) rebound occurred in only 3% of study participants receiving placebo. Together, these results show that although a waxing and waning symptom course may be common during recovery from acute COVID-19, symptom relapse with high-level viral rebound is rare in untreated persons.

In the analysis of the EPIC-HR phase 3 outpatient study of nirmatrelvir-ritonavir for mild to moderate COVID-19, an increase of 0.5 \log_{10} copies/mL or greater in nasal SARS-CoV-2 RNA levels from posttreatment levels was detected in approximately 4% of participants receiving placebo and 7% of participants receiving nirmatrelvir-ritonavir (8). However, viral RNA levels were quantified at only 2 follow-up time points (5 and 9 days after the end of nirmatrelvir-ritonavir treatment or placebo). In the ACTIV-2/A5401 trial, nasal RNA was quantified daily between days 0 and 14, which likely explains the substantially higher rates of viral rebound (31%) in our analysis. We could also define rates of viral rebound at differing viral load thresholds, with a 13% rate of high-level viral rebound using a viral load threshold associated with culture positivity (14).

Our finding that symptom rebound after initial improvement is also common during the disease course of untreated COVID-19 aligns with a prior analysis evaluating a smaller group of patients after complete symptom resolution (11). We also identified characteristics associated with the occurrence of symptom rebound, including female sex, having risk factors for severe disease, and having higher levels of nasal SARS-CoV-2 RNA shedding and symptom scores at study enrollment. The relapsing symptoms described here during acute SARS-CoV-2 infection have several potential causes. One possibility is that viral dissemination into different anatomical compartments over time could cause an evolving series of symptoms (12, 13). Another explanation is infection with 2 separate SARS-CoV-2 variants, which has been described but is still believed to be a rare occurrence (16). In addition, co-infection with another respiratory virus is a possibility, along with symptom rebound from a noninfectious cause. Given its high frequency, symptom rebound during acute COVID-19 is likely to be multifactorial. It should be noted that the duration of symptom and viral rebound observed in this study was short, 1 day in most cases. This is in contrast to the more prolonged symptom and viral rebound after nirmatrelvir-ritonavir treatment in previous case reports (3, 4, 15) that may indicate differences in the characteristics of the rebound episodes occurring with or without antiviral therapy, or bias in reported cases.

This study has limitations. In general, our observations could be affected by the underlying study population because the ACTIV-2/A5401 study enrolled a largely unvaccinated population infected with pre-Omicron variants. Of note, recently published studies have reported that neither vaccination nor Omicron variants substantially alter viral decay kinetics (14, 17). In addition, we did not include anosmia or ageusia in the symptom scoring because they have been reported to be of prolonged duration and may not resolve during the early recovery

period. Because the ACTIV-2/A5401 study did not enroll participants receiving nirmatrelvir-ritonavir, we cannot define rates of posttreatment viral or symptom rebound associated with this treatment. Another limitation is that this study did not include assessments of immune responses, and a maturing immune response reacting to the sudden reappearance of viral antigen could be an important contributory factor in symptomatic rebound (3, 5).

In summary, we observed that symptom and viral RNA rebound are individually common in participants who are not treated with antiviral agents. Our results highlight the importance of accounting for underlying rates of symptom relapse in the absence of antiviral therapy when evaluating the effects of antiviral treatments. However, in the absence of antiviral therapy, the co-occurrence of both symptom and high-level viral rebound was rare and the observed short-term symptom relapses were not generally indicative of greater infectivity. These results provide insight into the natural trajectory of viral rebound and symptom relapses during COVID-19, which is critical in the interpretation of studies reporting biphasic disease courses after nirmatrelvir-ritonavir or other antiviral treatment.

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Reproducible Research Statement: *Study protocol:* Available on request to the ACTIV-2 study team. *Statistical code:* All analyses were performed using code available in standard software packages. No new code was developed for this manuscript. *Data set:* Data are available under restricted access because of ethical restrictions. Access can be requested by submitting a data request at <https://submit.mis.s-3.net> and will require the written agreement of the AIDS Clinical Trials Group (ACTG) and the manufacturer of the investigational product. Requests will be addressed per ACTG standard operating procedures. Completion of an ACTG Data Use Agreement may be required.

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Author contributions are available at Annals.org.

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