STUDY A5401: SYMPTOM AND VIRAL REBOUND IN UNTREATED COVID-19 INFECTION

Ann Intern Med. doi:10.7326/M22-2381

ACTG

STUDY OBJECTIVE & BACKGROUND

Background:

- There are reports of people experiencing worsening symptoms and/or virologic rebound after completing nirmatrelvir-ritonavir (Paxlovid) treatment
  - This has been described in patients who did not receive nirmatrelvir-ritonavir
- There are few published studies on this issue

Objective:

Determine how common symptom or viral rebound of COVID-19 is in untreated outpatients. This is a secondary analysis from the ACTIV-2 participants in the placebo group.

- Primary analysis: Rebound after study day 0
- Secondary analysis: Rebound on or after study day 5

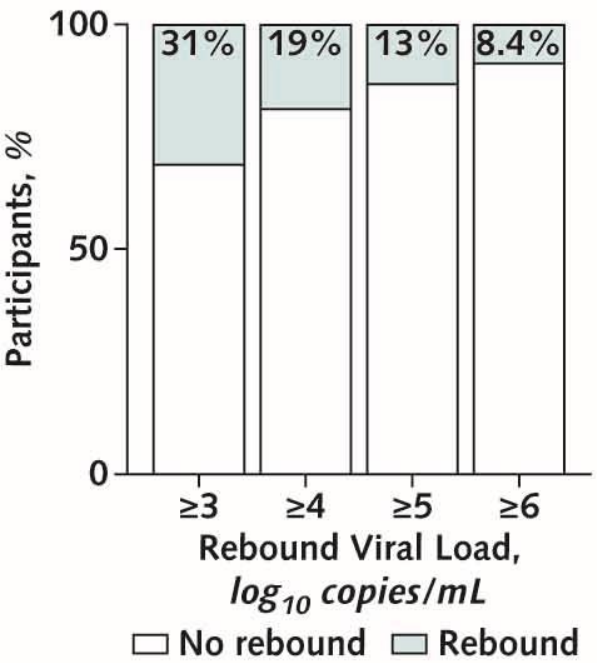
POPULATION OF THE STUDY

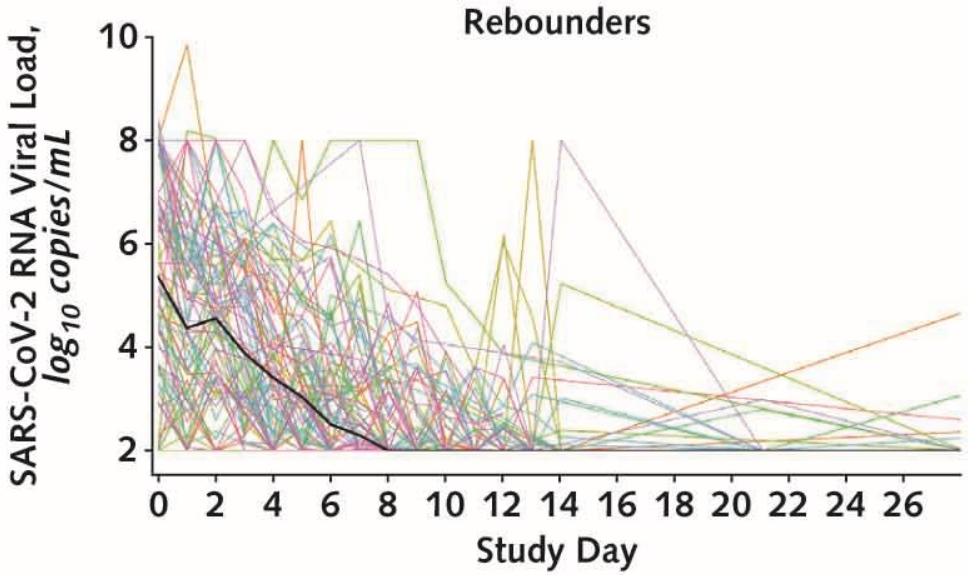
- Study population included 568 participants enrolled in ACTIV-2/A5401 trial who received placebo
- Viral rebound = ≥ 0.5 $\log_{10}$ viral RNA copies/mL
  - Anterior nasal swabs were collected days 0-14, 21, and 28
  - Symptom severity was recorded from day 0 – day 28
- Symptom rebound = 4-point total symptom score increase from baseline
  - Symptom score was calculated each day as the sum of scores for 13 targeted symptoms
    - Feverishness, cough, shortness of breath, sore throat, muscle pain, fatigue, headache, chills, nasal congestion, nasal discharge, nausea, vomiting, and diarrhea

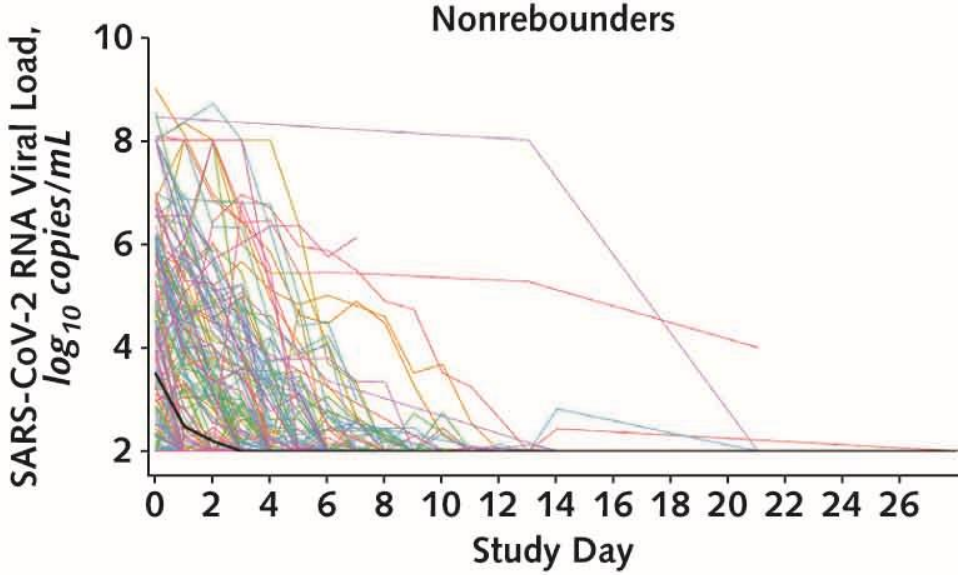
Table 1. Demographic Characteristics of Participants Categorized as Rebounders and Nonrebounders After Study Enrollment (Primary Analysis Definition)*

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)**

KEY RESULTS


100
50
0
Participants, %
31%
19%
13%
8.4%
≥3
≥4
≥5
≥6
Rebound Viral Load, log10 copies/mL
No rebound
Rebound


Rebounders
SARS-CoV-2 RNA Viral Load, log10 copies/mL
10
8
6
4
2
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Day


Nonrebounders
SARS-CoV-2 RNA Viral Load, log10 copies/mL
10
8
6
4
2
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Day

SUMMARY OF KEY FINDINGS

In ACTIV-2 participants who received no COVID-19 treatment:

- Symptom rebound was common (26%)
  - In most non-hospitalized participants, this was short and lasted 1 day
  - 1 in 4 ACTIV-2 participants showed symptom rebound
- Viral rebound was common (31%)
  - 1 in 8 ACTIV-2 participants showed high level viral rebound
- Combination of both viral load and symptom rebound was uncommon (<3%)

WHY IS THIS STUDY IMPORTANT? WHAT ARE THE NEXT RESEARCH STEPS?

- Without antiviral therapy, symptom or viral rebound in COVID-19 is common
- Rebound of symptoms after taking nirmatrelvir and ritonavir does not necessarily mean treatment failure

- Follow up studies may consider:
  - Evaluate persons that have been previously vaccinated, infected with Omicron and later variants to confirm findings in this study.
  - Assess symptom and viral rebound after antiviral treatment

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