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EVIDENCE BRIEF

Impact of SARS-CoV-2 Main Protease Mutations on Nirmatrelvir/Ritonavir (Paxlovid) Resistance

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Key Messages

- Nirmatrelvir is a novel protease inhibitor that binds to the main viral protease (M^{pro}) of SARS-CoV-2 to inhibit virus replication. Based on previous experience with HIV-1 resistance to protease inhibitors, there is concern regarding potential selection of nirmatrelvir-resistant SARS-CoV-2 strains following widespread use and/or underdosing of nirmatrelvir/ritonavir.
- In vitro data suggest that most of the Variants of Concern (VOC) and Variants of Interest (VOI) encountered before 2022 continue to be susceptible to nirmatrelvir/ritonavir despite their naturally occurring M^{pro} mutations. Clinical data suggests preserved susceptibility for the Delta variant.
- The current main Omicron sublineages (BA.1, BA.2, BA.3, BA.4, and BA.5) primarily have the P132H mutation; some additionally have the K90R mutation. Both mutations have no reported impact on nirmatrelvir activity in biochemical and cell culture assays.
- Treatment-emergent M^{pro} mutations have been described in clinical trials, however, the potential impact of these mutations on treatment response is currently unknown. Therefore, ongoing monitoring of mutation emergence through population-based or targeted sequencing surveillance is needed.

Issue and Scope

This document summarizes a rapid review of currently available literature related to the impact of previously reported SARS-CoV-2 main protease (M^{pro}) mutations on nirmatrelvir/ritonavir in vitro activity and treatment response.

Background

Nirmatrelvir (PF-07321332) is a novel protease inhibitor that binds to the main viral protease (M^{pro}, also known as $3CL^{pro}$ or nsp5) of SARS-CoV-2 to inhibit virus replication. Ritonavir is a potent cytochrome P450 3A (CYP3A) inhibitor that increases serum concentrations of nirmatrelvir. Combined, nirmatrelvir/ritonavir (Paxlovid) has been demonstrated to be effective in reducing the risk of hospitalization among unvaccinated individuals with COVID-19.[1] On January 17, 2022, Health Canada authorized nirmatrelvir/ritonavir for the treatment of mild COVID-19 in individuals at high risk for progression to severe illness.[2]

Based on previous experience with HIV-1 resistance to protease inhibitors, there is concern that nirmatrelvir/ritonavir overuse and/or underdosing could lead to the selection of nirmatrelvir-resistant SARS-CoV-2 strains.[3] Drug interactions between nirmatrelvir/ritonavir and potent CYP3A inducers, leading to decreased nirmatrelvir/ritonavir serum concentrations, have also been identified as a potential risk for the development of nirmatrelvir resistance.[4,5]

In the HIV-1 context, some protease mutations are known to cause impaired treatment response while other mutations cause improved treatment response; some mutations have no clinical impact as well.[6] With SARS-CoV-2, the prevalence and impact of M^{pro} mutations is only starting to be elucidated.[5] Both *in vitro* and clinical studies are required to address whether, and which, SARS-CoV-2 M^{pro} mutations can influence nirmatrelvir/ritonavir treatment response.

Methods

To identify relevant evidence on this topic, scientific literature searches in MEDLINE (Ovid platform), Embase (Ovid platform), BIOSIS Previews (Ovid platform), and Scopus (Elsevier platform) were conducted on May 17, 2022 by PHO Library Services. On the same day, searches for scientific literature and preprints were run in the National Institutes of Health iSearch COVID-19 Portfolio, which includes content from the following preprint servers: arXiv, bioRxiv, ChemRxiv, medRxiv, Preprints.org, Qeios, and Research Square. Additionally, a grey literature search was conducted on June 1, 2022. The grey literature search included clinical trial registration records (ClinicalTrials.gov), a site search of the Pfizer website for posted trial results, use of a custom search engine to retrieve reports from international public health agencies, and a web search for other types of grey literature (e.g., media coveage). Search strategies were developed and peer-reviewed by members of the PHO Library Services team, and are available upon request.

Findings

Prevalence of naturally occurring M^{pro} mutations

- Prior to the global distribution of nirmatrelvir/ritonavir in January 2022, approximately 4,800 naturally occurring mutations modifying 291 of the 306 amino acids comprising the M^{pro} protein have been documented in SARS-CoV-2 lineages.[7,8] Most of the identified mutations are rare, with only 19 mutations detected in ≥ 0.1% of SARS-CoV-2 sequences reported in the global GISAID database (see Table 1).[9]

Table 1: Most prevalent M^{pro} mutations in GISAID database from January 2020 to January 2022

M^{pro} mutation	Associated variant(s)	M^{pro} mutation	Associated variant(s)
G15S	Lambda	**P132L**	Alpha and Delta
T21I	B.1.1.318	**V157L**	Delta
V73I	Delta	**A191V**	Alpha and Delta
L75F	Alpha and Delta	**T196M**	Epsilon and Delta
K88R	Delta	**L205V**	Zeta
L89F	B.1.2	**V212F**	Delta
K90R	Alpha, Beta, and Delta	**L220F**	Delta
P108S	Alpha and Delta	**I259L**	Delta
A129V	Alpha and Delta	**A260V**	Alpha and Delta
P132H	Omicron		

In vitro impact of M^{pro} mutations on nirmatrelvir activity

- In November 2021, the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) evaluated the effect of 48 M^{pro} mutations on nirmatrelvir potency using biochemical enzymatic assays. The evaluation included some of the naturally occurring mutations listed in Table 1 as well as artificially generated mutations (not previously reported in GISAID) for exploratory analysis. Compared to wild-type M^{pro}, 17 mutations were linked with a 1- to 3-fold reduction of nirmatrelvir potency, and 10 mutations had > 3-fold reduction in potency (see Table 3).[10-12]

- Cell culture antiviral activity of nirmatrelvir to common SARS-CoV-2 variants has also been evaluated through CDER. Nirmatrelvir was able to inhibit viral replication of all cultured variants despite their known M^{pro} mutations, including B.1.1.318, B.1.2, C.37 (Lambda), B.1.621 (Mu), P2 (Zeta), B.1.1.7 (Alpha), P.1 (Gamma), B.1.617.2 (Delta), and B.1.1.529.1 (Omicron BA.1). Only B.1.351 (Beta) showed reduced activity of nirmatrelvir in cell cultures (3-fold reduction in activity).[8,10,13-16] Animal studies of hamsters infected with B.1.1.529.2 (Omicron BA.2) have also shown successful inhibition of BA.2 viral replication using nirmatrelvir.[14,17]

- A cell culture resistance selection study by CDER has used nirmatrelvir-susceptible betacoronavirus surrogates (mouse hepatitis viruses) grown under increasing doses of nirmatrelvir to identify potential treatment-emergent mutations. The emergence of six mouse hepatitis virus M^{pro} mutations has been reported, with SARS-CoV-2 M^{pro} amino acid equivalents shown in brackets here: P15A (G15A), T50K (L50K), P55L (E55L), F126L (Y126L), T129M (A129M), and S144A (S144A).[12]

- Another cell culture resistance selection study by Zhou et al. has used wild-type SARS-CoV-2 strains grown under increasing doses of nirmatrelvir. The emergence of two mutant strains, one with single E166V mutation and one with combined L50V and E166V mutations, was reportedly associated with up to 80-fold reduction in nirmatrelvir cell culture activity.[18] The E166V mutation was hypothesized to contribute to most of the resistance phenotype identified, whereas L50V was hypothesized to lower the fitness cost incurred by the E166V mutation.

- Another cell culture resistance selection study by Jochmans et al., using wild-type SARS-CoV-2 strains grown under increasing doses of an experimental proteinase inhibitor (ALG-097161), culminated in the selection of a triple mutant strain expressing L50V, E166A, and L167F.[19] The triple mutant strain was then assessed for cross-resistance to nirmatrelvir and was found to have up to 51-fold reduction in nirmatrelvir cell culture activity. The combined L50V-E166A-L167F mutation profile was also evaluated using biochemical enzymatic assays and was found to have a 72-fold reduction in nirmatelvir potency (versus 10-fold and 4-fold reduction, respectively, for individual E166A and L167F mutations as per Table 3).

Clinical impact of M^{pro} mutations on treatment efficacy

- The Pfizer-sponsored Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) clinical trial evaluated the clinical efficacy of nirmatrelvir/ritonavir and was found to reduce hospitalization risk by 89%.[1,16] Anecdotally, 98% of EPIC-HR study participants were infected with the Delta variant, although no sub-analysis was performed to evaluate the relative efficacy of nirmatrelvir/ritonavir depending on infected variant.[20] A similar study performed during an Omicron BA.2.2 wave in Hong Kong (no confirmatory sequencing data available) showed a 31% reduction in hospitalization risk, representing a lower efficacy than reported by EPIC-HR with Delta-predominant cases.[21]

- The EPIC-HR trial prospectively collected sequencing data at baseline and post-treatment for 361 nirmatrelvir/ritonavir-treated participants and 402 placebo-treated participants. 33 unique M^{pro} mutation events were identified in the treatment group post-nirmatrelvir/ritonavir (see Table 2). None of the participants with treatment-emergent mutations where hospitalized. The clinical significance of these mutations is not known, as some of these mutations have also been reported to naturally occur in lineages without nirmatrelvir exposure. Furthermore, some of these emergent mutations (P132L, P132S, A260V, and A266V) were evaluated in biochemical assays and no loss of nirmatrelvir potency was found.[1]

- Recent case reports have described recurrent illness in non-immunocompromised individuals several days after completing a 5-day course of nirmatrelvir/ritonavir for laboratory confirmed SARS-CoV-2 infection. The mechanism and clinical implications of these nirmatrelvir/ritonavir-treated rebound events is not yet clear, however COVID-19 rebound has not yet been associated with detection of M^{pro} mutations.[22-25]

- Due to the current lack of data regarding the frequency and clinical impact of treatment-emergent mutations, further nirmatrelvir/ritonavir clinical studies integrating sequencing data of treated participants are needed.[5] A search of clinical trial registries identified only one study planning to evaluate virological criteria linked to the emergence of resistance (i.e., proportion of patients developing treatment-escape variants, with genotypic and phenotypic characterization of resistance variants). No additional information on this study is publicly available as is it currently in the recruitment phase.[26]

Table 2: Treatment-emergent M^{pro} mutations identified during EPIC-HR trial (n = 361 treated participants)

Emergent M^{pro} mutation	No. of participants	Emergent M^{pro} mutation	No. of participants
A7S, A7T, or A7V	3	**E166V**	3
L30F	3	**T196A, T196K, T196M, or T196R**	4
M82I or M82R	3	**W207L, W207S, or W207del**	5
G109E, G109R, or G019V	3	**A260D, A260T, or A260V**	8
P132L or P132S	4	**D263E**	3
C145F, C145R or C145Y	3	**A266P or A266V**	3
D153H or D153Y	3	**V297A, V297F, or V297del**	3

Population-based genomic surveillance of M^{pro} mutations

- Since January 2022, there has been increased interest in genomic surveillance to track M^{pro} mutations arising from antiviral selection pressure. The UK COVID-19 Genomics Consortium Mutation Explorer (COG-UK/ME) is a publicly available online tool that reports on the prevalence in the UK of some M^{pro} mutations. 10 M^{pro} mutations having decreased *in vitro* nirmatrelvir activity (based on the CDER biochemical assays) are routinely reported. Table 3 lists the current cumulative prevalence of the selected mutations out of a total of 2,730,440 UK sequences. Of note, in the 28 days preceding June 9, 2022, only two cases were detected (both with G15S mutation).[27]

Table 3: M^{pro} mutations leading to reduced nirmatrelvir potency in biochemical assays and cumulative detection of selected Mpro mutations in COG-UK/ME up to June 9, 2022

M^{pro} mutation	Fold reduction in nirmatrelvir potency	Cumulative detection in COG-UK/ME (n= 2,730,440 sequences)
G15S	4-fold	**7140**
Y54A	24-fold	**0**
T135I	3-fold	**4**
F140A	39-fold	**0**
S144A	92-fold	**8**
H164N	6-fold	**0**
E166A	10 to 33-fold	**1**
L167F	4-fold	**Not monitored**
H172Y	233-fold	**1**
Q189K	65-fold	**5**
D248E	4-fold	**743**

- In Ontario, the data from samples collected, between November 27, 2021, to June 3, 2022, and sequenced at Public Health Ontario (PHO)'s laboratory were reviewed for M^{pro} mutation rates (unpublished data).
    - A total of 22,900 sequences were evaluated within PHO, which did not include sequences from other laboratories participating in the Ontario COVID-19 Genomics Network.
    - Table 4 lists the cumulative detection of some M^{pro} mutations of interest based on their biochemical, cell culture, resistance selection, and/or clinical evidence so far reported. Of note, due to the limited evidence available, the importance of these mutations is not yet fully defined as no clinical failures with these mutations have been reported to date. Only three mutations of interest were detected in PHO's sequencing data during the 6-month period: A7T (n = 20), G15S (n = 1), and D263E (n = 3).

- In addition to the mutations of interest listed in Table 4, other mutations that have not yet been evaluated for *in vitro* or clinical resistance were found in the PHO sequencing data. These mutations may represent naturally occurring polymorphisms but warrant further studies. The following mutations were identified in more than two sequences: T24I (n = 4), N84S (n = 3), T93I (n = 7), F103L (n = 4), A116V (n = 4), P184S (n = 29), P184L (n = 4), A193T (n = 3), F223L (n = 4), K236R (n = 3), P241L (n = 3), G283S (n = 6), A285V (n = 3), and A285T (n = 17).

- Otherwise, the mutations K90R (n = 407) and P132H (n = 22,8264) were the most prevalent M^{pro} mutations found in PHO sequences, however these two mutations are not expected to lead to resistance based on the CDER biochemical and cell culture studies.

Table 4: Cumulative detection of selected Mpro mutations of interest at PHO from November 27, 2021, to June 3, 2022

M^{pro} mutation	Current evidence*	Cumulative detection (n = 22,900 sequences)	Associated lineage(s) (within-lineage rate)
A7T	D	20	BA.1.1 (0.20%)
A7S or A7V	D	0	None
G15S or G15A	A, C	1	BA.1.1 (0.01%)
L30F	D	0	None
L50K	C	0	None
Y54A	A	0	None
M82I or M82R	D	0	None
G109E, G109R, or G019V	D	0	None
Y126L	C	0	None
A129M	C	0	None
T135I	A	0	None
F140A	A	0	None
S144A	A, C	0	None
C145F, C145R or C145Y	D	0	None

M^{pro} mutation	Current evidence*	Cumulative detection (n = 22,900 sequences)	Associated lineage(s) (within-lineage rate)
D153H or D153Y	D	0	None
E166V or E166A	A, D	0	None
L167F	A	0	None
H172Y	A	0	None
Q189K	A	0	None
T196A, T196K, T196M, or T196R	D	0	None
W207L, W207S, or W207del	D	0	None
D248E	A	0	None
A260T or A260D	D	0	None
D263E	D	3	BA.1.1 (0.03%)
A266P	D	0	None
V297A, V297F, or V297del	D	0	None

*Legend: A, biochemical assay, see Table 3; B, cell culture assay, see text; C, resistance selection study, see text; D, post-treatment emergence, see Table 2.

Conclusion

Current *in vitro* data suggest that most of the VOCs and VOIs encountered prior to 2022 remain susceptible to nirmatrelvir/ritonavir despite their naturally occurring M^{pro} mutations. Clinical data further suggest preserved susceptibility for the Delta variant, with additional clinical studies required to confirm treatment efficacy against currently circulating Omicron variants.

Some M^{pro} mutations have been hypothesized to reduce nirmatrelvir efficacy based on either reduced enzymatic potency, reduced antiviral activity in cell cultures, or emergence in resistance selection studies. Some treatment-emergent M^{pro} mutations have also been described during clinical trials. However, the extent to which these mutations could negatively impact treatment response has not yet been elucidated.

The current main Omicron sublineages (BA.1, BA.2, BA.3, BA.4, and BA.5) primarily have the P132H mutation, and some additionally have the K90R mutation, both of which have no reported impact on nirmatrelvir activity in biochemical and cell culture assays. The mutations of interest A7T, G15S, and D263E have also rarely been found in Ontario in BA.1.1 variants, yet their clinical relevance is not yet known. Some rarer and unevaluated mutations have also been identified and their impact on treatment requires further studies. Furthermore, the *in vitro* and *in vivo* selective emergence of mutations following nirmatrelvir exposure warrants ongoing monitoring of mutation emergence through population-based or targeted sequencing surveillance.

References

1. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med. 2022;386(15):1397-408. Available from: https://doi.org/10.1056/NEJMoa2118542

2. Health Canada. Health Canada authorizes PAXLOVID for patients with mild to moderate COVID-19 at high risk of developing serious disease [Internet]. Ottawa, ON: Government of Canada; 2022 [cited 2022 Jun 1]. Available from: https://www.canada.ca/en/health-canada/news/2022/01/health-canada-authorizes-paxlovidtm-for-patients-with-mild-to-moderate-covid-19-at-high-risk-of-developing-serious-disease.html

3. Shah D, Freas C, Weber IT, Harrison RW. Evolution of drug resistance in HIV protease. BMC Bioinformatics. 2020;21(18):1-15. Available from: https://doi.org/10.1186/s12859-020-03825-7

4. Pfizer Canada ULC; Health Canada. Product monograph including patient medication information: PAXLOVID (Submission Control Number: 261884) [Internet]. Ottawa, ON: Government of Canada; 2022 [cited 2022 Jun 1]. Available from: https://covid-vaccine.canada.ca/info/pdf/paxlovid-pm-en.pdf

5. Mótyán JA, Mahdi M, Hoffka G, Tőzsér J. Potential resistance of SARS-CoV-2 main protease (Mpro) against protease inhibitors: lessons learned from HIV-1 protease. Int J Mol Sci. 2022;23(7):3507. Available from: https://doi.org/10.3390/ijms23073507

6. Mata-Munguía C, Escoto-Delgadillo M, Torres-Mendoza B, Flores-Soto M, Vázquez-Torres M, Gálvez-Gastelum F, et al. Natural polymorphisms and unusual mutations in HIV-1 protease with potential antiretroviral resistance: a bioinformatic analysis. BMC Bioinformatics. 2014;15(1):1-17. Available from: https://doi.org/10.1186/1471-2105-15-72

7. Lee JT, Yang Q, Gribenko A, Perrin BS, Zhu Y, Cardin R, et al. Genetic surveillance of SARS-CoV-2 Mpro reveals high sequence and structural conservation prior to the introduction of protease inhibitor Paxlovid. bioRxiv 486331 [Preprint]. 2022 Mar 30 [cited 2022 Jun 13]. Available from: https://doi.org/10.1101/2022.03.29.486331

8. Ullrich S, Ekanayake KB, Otting G, Nitsche C. Main protease mutants of SARS-CoV-2 variants remain susceptible to nirmatrelvir. Bioorg Med Chem Lett. 2022;62:128629. Available from: https://doi.org/10.1016/j.bmcl.2022.128629

9. GISAID Initiative. GISAID [Internet]. Munich: Freunde von GISAID; 2022 [cited 2022 Jun 15]. Available from: https://www.gisaid.org/

10. Greasley SE, Noell S, Plotnikova O, Ferre R, Liu W, Bolanos B, et al. Structural basis for the in vitro efficacy of nirmatrelvir against SARS-CoV-2 variants. J Biol Chem. 2022;298(6):101972. Available from: https://doi.org/10.1016/j.jbc.2022.101972

11. Sacco MD, Hu Y, Gongora MV, Meilleur F, Kemp MT, Zhang X, et al. The P132H mutation in the main protease of Omicron SARS-CoV-2 decreases thermal stability without compromising catalysis or small-molecule drug inhibition. Cell Res. 2022;32(5):498-500. Available from: https://doi.org/10.1038/s41422-022-00640-y

12. Pfizer Labs, United States Food and Drug Administration. Emergency Use Authorization (EUA) for Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets) - Center for Drug Evaluation and Research (CDER) review [Internet]. Silver Springs, MD: US Department of Health and Human Services; 2021 [cited 2022 Jun 13]. Available from: https://www.fda.gov/media/155194/download

13. Li P, Wang Y, Lavrijsen M, Lamers MM, de Vries AC, Rottier RJ, et al. SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination. Cell Res. 2022;32:322-4. Available from: https://doi.org/10.1038/s41422-022-00618-w

14. Kawaoka Y, Uraki R, Kiso M, Iida S, Imai M, Takashita E, et al. Characterization and antiviral susceptibility of SARS-CoV-2 Omicron/BA.2. Res Sq 1275091 [Preprint]. 2022 Feb 24 [cited 2022 Jun 3]. Available from: https://doi.org/10.21203/rs.3.rs-1375091/v1

15. Vangeel L, Chiu W, De Jonghe S, Maes P, Slechten B, Raymenants J, et al. Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. Antiviral Res. 2022:105252. Available from: https://doi.org/10.1016/j.antiviral.2022.105252

16. Pfizer Labs, US Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization for Paxlovid™ [Internet]. Silver Springs, MD: US Department of Health and Human Services; 2022 [cited 2022 Jun 13]. Available from: https://www.fda.gov/media/155050/download

17. Uraki R, Kiso M, Iida S, Imai M, Takashita E, Kuroda M, et al. Characterization and antiviral susceptibility of SARS-CoV-2 Omicron/BA. 2. Nature. 2022:1-3. Available from: https://doi.org/10.21203/rs.3.rs-1375091/v1

18. Zhou Y, Anbro Gammeltoft K, Abildgaard Ryberg L, Pham LV, Fahnøe U, Binderup A, et al. Nirmatrelvir resistant SARS-CoV-2 variants with high fitness in vitro. bioRxiv 494921 [Preprint]. 2022 Jun 7 [cited 2022 Jun 9]. Available from: https://doi.org/10.1101/2022.06.06.494921

19. Jochmans D, Liu C, Donckers K, Stoycheva A, Boland S, Stevens S, et al. The substitutions L50F, E166A and L167F in SARS-CoV-2 3CLpro are selected by a protease inhibitor *in vitro* and confer resistance to nirmatrelvir. bioRxiv 495116 [Preprint]. 2022 Jun 7 [cited 2022 Jun 9]. Available from: https://doi.org/10.1101/2022.06.07.495116

20. Hicks L, Hodowanec A, Shepard C, Pau AK, Troy S. What clinicians need to know about the new oral antiviral medications for COVID-19 [Webinar]. Atlanda, GA: Centers for Disease Control and Prevention, Centre for Preparedness and Response Clinician Outreach and Communication Activity Call; 2022 [presented 2022 Jan 12; cited 2022 Jun 29]. Available from: https://emergency.cdc.gov/coca/ppt/2022/011222_slide.pdf

21. Wong CKH, Au ICH, Lau KT, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir/ritonavir against mortality, hospitalization, and in-hospital outcomes among community-dwelling, ambulatory COVID-19 patients during the BA. 2.2 wave in Hong Kong: an observational study. medRxiv 22275631 [Preprint]. 2022 May 26 [cited 2022 Jun 13]. Available from: https://doi.org/10.1101/2022.05.26.22275631

22. Centers for Disease Control and Prevention, Health Alert Network. HAN archive 00467: COVID-19 rebound after Paxlovid treatment [Internet]. Atlanta, GA: United States Department of Health and Human Services; 2022 [cited 2022 Jun 1]. Available from: https://emergency.cdc.gov/han/2022/han00467.asp

23. Boucau J, Uddin R, Marino C, Regan J, Choudhary MC, Flynn JP, et al. Virologic characterization of symptom rebound following nirmatrelvir-ritonavir treatment for COVID-19. medRxiv 22275326 [Preprint]. 2022 May 26 [cited 2022 Jun 1]. Available from: https://doi.org/10.1101/2022.05.24.22275326

24. Charness M, Gupta K, Stack G, Strymish J, Adams E, Lindy D, et al. Rapid relapse of symptomatic Omicron SARS-CoV-2 infection following early suppression with Nirmatrelvir/Ritonavir. Res Sq 1588371 [Preprint]. 2022 May 23 [cited 2022 Jun 1]. Available from: https://doi.org/10.21203/rs.3.rs-1588371/v3

25. Carlin AF, Clark AE, Chaillon A, Garretson AF, Bray W, Porrachi M, et al. Virologic and immunologic characterization of COVID-19 recrudescence after Nirmatrelvir/Ritonavir treatment. Res Sq 1662783 [Preprint]. 2022 May 18 [cited 2022 Jun 1]. Available from: https://doi.org/10.21203/rs.3.rs-1662783/v1

26. ClinicalTrials.gov. Prevention of COVID-19 complications in high-risk subjects infected by SARS-CoV-2 and eligible for treatment under a cohort ATU ('Autorisation Temporaire d'Utilisation') OR or Authorisation for Early Access (AAP): a prospective cohort. ClinicalTrials.gov Identifier: NCT04885452 [Internet]. Bethesda, MD: United States National Library of Medicine; 2022 [cited 2022 Jun 1]. Available from: https://clinicaltrials.gov/ct2/show/NCT04885452

27. Wright DW, Harvey WT, Hughes J, Cox M, Peacock TP, Colquhoun R, et al. Tracking SARS-CoV-2 mutations and variants through the COG-UK-mutation explorer. Virus Evol. 2022;8(1):veac023. Available from: https://doi.org/10.1093/ve/veac023

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