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Review Article

Update on Early Combination Therapy with Lastest Monoclonal Antibodies and Antivirals as HIV, HCV, Influenza in Extremely Vulnerable Persons with Sars-Cov-2: A Literature Review and Clinical Experience

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Abstract

The emergence of new variants of concern in immunocompromised persons with SARS-CoV-2, particularly those with mutations in the spike protein, has complicated treatment strategies.

Some Therapies focused only on viral clearance effects and not on major clinical outcomes.

As the virus continues to evolve, the development of broad-spectrum therapies, along with personalized approaches to treatment, will be crucial in managing COVID-19 .

After the first year period in which several treatments were employed early intervention strategies, including the use of antiretrovirals and monoclonal antibodies, have emerged as promising approaches to mitigate the severity of COVID-19 in fragile individuals and prevent disease progression, hospitalization and death even in recent time with less aggressive SARS-CoV-2 variants.

Guidelines, high-quality data for combination treatment exploiting antivirals and neutralizing antibodies do not exist in the outpatient setting, especially in severe immunocompromised individuals.

Nevertheless, several studies have attempted to investigate the efect of this approach and although these are often observational studies without control groups, generally no severe adverse reactions from the combination therapy have been reported.

The potential efficacy of early combination therapy, based on an antiviral plus a monoclonal antibody, for COVID-19 in severely immunocompromised patients is matter of clinical and literature debate in the scientific word.

To date, information concerning the early treatments of COVID-19 using combined therapies has been limited.

In this Literature Review we explain the Last variant of concern and the updates on combination therapy for vulnerable persons with Sars-Cov-2.

Keywords: Early Combination Therapy; Sars-Cov-2; New COVID-19 Variants; Vulnerable Patients

Introduction

The emergence of new variants of concern among immunocompromised persons infected with SARS-CoV-2, specifically those exhibiting changes in the spike protein, has introduced challenges to treatment protocols. Some therapeutic approaches have concentrated solely on clearing the virus without considering significant clinical outcomes. As the virus proceeds to mutate, the creation of broad-spectrum treatments and tailored approaches will be critical for the effective management of COVID-19. In the first year following the outbreak, various treatment modalities were applied and early intervention strategies, such as antiretroviral medications and monoclonal antibodies, have demonstrated the potential to mitigate the effects of COVID-19 in

individuals with weakened immune systems, thereby assisting in the prevention of disease advancement, reducing hospitalization and minimizing mortality, particularly with less severe variants of SARS-CoV-2.

Nevertheless, there is a scarcity of high-quality data regarding combination therapies employing antivirals and neutralizing antibodies outside of hospital environments, especially for those facing severe immune deficiencies. Despite this, many research initiatives have examined the viability of this approach and while most of these studies are observational and lack control groups, substantial adverse effects from the combination therapies have generally not been reported.

The potential effectiveness of early combination treatment involving an antiviral agent alongside a monoclonal antibody for the management of COVID-19 in patients with significant immune compromise remains a subject of ongoing research and debate among scientists. Currently, there is limited data regarding the early administration of mixed therapies for treating COVID-19.

This literature review will address the most recent variants of concern and provide the latest information on combination therapy for vulnerable individuals affected by SARS-CoV-2.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Early Combination Therapy in Sars-Cov-2 Patients as HIV, HCV and Influenza

While the use of antiviral combination has shown an important effectiveness in managing chronic viral infections diseases, such as HIV and HCV, applying this approach to acute infections like influenza and COVID-19 is just beginning to be explored. A rationale for utilizing drugs with different action mechanisms is to reduce the risk of developing drug resistance, which is a significant concern with chronic viral infections. Nevertheless, instances of rapid development of drug resistance have also been noted when SARS-CoV-2 is exposed to monoclonal antibodies or direct-acting antivirals, especially in immunocompromised individuals needing extended treatment. Currently, combination therapy for SARS-CoV-2 is primarily restricted to monoclonal antibody combinations, including casirivimab/imdevimab, bamlanivimab/etesevimab and CIL/TIX, yet these combinations all target the same replication stage of the virus [1].

Even though there have been anecdotal reports of administering two anti-SARS-CoV-2 therapies together in clinical practices, it is improbable that clinical trials will be devised to compare combinations of medications against single anti-SARS-CoV-2 treatments. Therefore, assessing the potential synergistic effects of various drugs in vitro is essential at this juncture.

It is worth mentioning that prioritizing in vitro data over the harder-to-acquire in vivo information is not a new phenomenon in the realm of SARS-CoV-2 treatments. The authorization of certain monoclonal antibodies has frequently been revoked based on in vitro evidence of ineffectiveness rather than from clinical trial data, particularly due to the emergence of new viral variants.

Evaluating the dose-response relationship of drug combinations requires assessing the inhibition of viral replication within a controlled virus-cell system, where various concentrations of the selected drugs are tested together. Synergistic interactions are formally identified by activity scores that exceed the combined effects of the individual drugs. Numerous online resources are available, utilizing diverse mathematical models to classify combinatorial effects as synergy, additivity or antagonism such as MacSynergy II™, CompuSyn, Combenefit and SynergyFinder.

These tools vary, ranging from straightforward spreadsheet systems to more sophisticated software programs with a graphical interface that incorporate machine learning algorithms. Given the lack of consensus on how synergy is defined, it is crucial to conduct post hoc analyses to identify the specific drug concentrations that yield clear evidence of synergy. In fact, utilizing the latest version of the well-known SynergyFinder, we identified significant synergistic potency variations at particular concentrations of the tested drug combinations, tested, although summary weighted SS indicated additive effects only and notably, we could largely support this indication using confirmatory laboratory tests [1,2].

Update on SARS-CoV-2 Variants of Concern as of 20 December 2024

Source: European Centre for Disease Prevention and Control

An agency of the European Union. Surveillance and Updates on COVID-19 December 2024 [2].

Variant classification serves as an important communication tool for alerting EU/EEA countries about the emergence of SARS-CoV-2 variants with concerning properties likely to impact the epidemiological situation in the EU/EEA.

The ECDC Strategic Analysis of Variants in Europe (SAVE) Working Group is a multidisciplinary team comprising of ECDC Experts working in Respiratory Viruses, Microbiology, Bioinformatics, Mathematical Modelling, Epidemic Intelligence, Emergency Preparedness and Response and Vaccine-Preventable Diseases and Immunisation. Currently meetings are held once per month to assess the observed or predicted impact of currently circulating and newly emerging SARS-CoV-2 variants in the EU/EEA and globally.

ECDC utilises three categories of variant classification to communicate increasing levels of concern about a new or emerging SARS-CoV-2 variant: Variant Under Monitoring (VUM), Variant of Interest (VOI) and Variant of Concern (VOC). Classification criteria and recommended Member state actions are available here:

ECDC variant classification criteria and recommended Member State actions

New evidence is regularly assessed on variants detected through epidemic intelligence, genomic horizon scanning or other scientific sources. If a decision is made to add, remove or change the category for any variant, the tables are updated to reflect this change. The tables are regularly sent for consultation to ECDC stakeholders, such as the European Commission and WHO Regional Office for Europe's joint virus characterisation working group.

Variant surveillance data, including the distribution of VOC and VOI variant proportions in the EU/EEA and detailed country-specific COVID-19 epidemiological updates are available as part of the European Respiratory Virus Surveillance Summary (ERVISS).

Useful links

Slides from the most recent SAVE WG meeting are available in EpiPulse, with SARS-CoV-2 variant classification updates also published in ECDC's Communicable Disease Threats Reports.

To review a timeline of variant classification decisions, visit our change log.

Following classification of a VOC or VOI, multiple closely related sub-lineages may emerge. To facilitate reporting of variant detections by countries to TESSy, a table listing sub-lineages assigned to VOCs and VOIs as of 5 December 2024 is available here.

An additional table that includes sub-lineages assigned to VUMs as of 5 December 2024 is available here.

Description of the Tables

The Table 1-3 include:

Category: Variant of Concern (VOC), Variant of Interest (VOI) or Variant Under Monitoring (VUM).

1. *WHO label:* As of 31st May 2021, WHO proposed labels for global SARS-CoV-2 variants of concern and variants of interest to be used alongside the scientific nomenclature in communications about variants to the public. This list includes variants on WHO's global list of VOC and VOI and is updated as WHO's list changes.
2. *Lineage and additional mutations:* The variant designation specified by one or more Pango lineages and any additional characteristic spike protein changes. An alternate description may be used if the variant is not easy to describe using this nomenclature. For updated information on Pango lineages and definition of lineages and for instructions on how to suggest new lineages, visit the Pango lineages website. Each lineage in then table is linked to the respective lineage page on the Pango lineages website.
3. *Country first detected:* Only present if there is moderate confidence in the evidence relating to the first country of detection.
4. *Spike mutations of interest:* not all spike protein amino acid changes are included – this is not a full reference for assignment of the variants. It includes changes to spike protein residues 319-541 (receptor binding domain) and 613-705 (the S1 part of the S1/S2 junction and a small stretch on the S2 side) and any additional unusual changes specific to the variant.
5. *Year and month first detected:* As reported in the GISAID EpiCoV database. This can be adjusted backwards in time if new retrospective detections are made.

6. *Evidence* concerning properties in three different categories:
   - Transmissibility
   - Immunity
   - Infection severity

Each category is annotated as increased, reduced, similar, unclear or no evidence depending on the currently available evidence. Increased or reduced means that there is evidence demonstrating that the property is different enough for the variant compared to previously circulating variants that it is likely to have an impact on the epidemiological situation in the EU/EEA. Similar means that there is evidence that demonstrates that the property is not different enough for this variant compared to previously circulating variants that it is unlikely to have an impact. Unclear means that the current evidence is preliminary or contradictory enough to make the assessment uncertain. No evidence means that no evidence has yet been evaluated for this category. The evidence is further annotated with v or m to indicate whether the evidence is available for the variant itself (v) or for mutations associated with the variant (m).

7. *Transmission in the EU/EEA:* Categorised as dominant, community, outbreak(s) and sporadic/travel. The categories are qualitative and the assessment is based on surveillance data collected in TESSy, GISAID EpiCoV data, epidemic intelligence data and direct communications with the affected countries.

Variants of Concern (VOC)

As of 3 March 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 variants of concern (VOC), as these parental lineages are no longer circulating. ECDC will continue to categorise and report on specific SARS-CoV-2 sub-lineages in circulation that are relevant to the epidemiological situation. There are currently no SARS-CoV-2 variants meeting the VOC criteria.

Variants of Interest (VOI)

All sub-lineages of the listed lineages are also included in the variant. For the full list of lineages, please look at the Table 1.

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	BA.2.86	n/a	I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, F486P	n/a	Baseline (6)	Baseline (6-8)	Baseline	Community
Omicron	KP.3	n/a	Q493E, F456L	n/a	No evidence	No evidence	No evidence	Dominant

Table 1: Variants of Interest (VOI).

Variants Under Monitoring

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	XEC	n/a	T22N, F59S, F456L, Q493E, V1104L	n/a	No evidence	No evidence	No evidence	Community

Table 2: Variants under monitoring.

De-escalated Variants

These additional variants of SARS-CoV-2 have been de-escalated based on at least one the following criteria: (1) the variant is no longer circulating, (2) the variant has been circulating for a long time without any impact on the overall epidemiological situation, (3) scientific evidence demonstrates that the variant is not associated with any concerning properties.

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Alpha	B.1.1.7	United Kingdom	N501Y, D614G, P681H	September 2020	Increased (v) (9)	Similar	Increased (v) (10, 11)	Drastically reduced circulation in the EU/EEA following the emergence of Delta; little evidence of impact on vaccine

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								induced immunity
n/a	B.1.1.7+E484K	United Kingdom	E484K, N501Y, D614G, P681H	December 2020	Increased (v) (9)	Increased (v) (12, 13)	Increased (v) (10)	Very low levels of circulation in the EU/EEA
Epsilon	B.1.427/B.1.429	USA	L452R, D614G	September 2020	Unclear (14)	Increased (v) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA and available data indicating that vaccines and treatments are effective against such variant
n/a	B.1.616*(c)*	France	V483A, D614G, H655Y, G669S	February 2021	Detection (c) (15)	No evidence	No evidence	Not detected since 2021-04-23 (16)

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Eta	B.1.525	Nigeria	E484K, D614G, Q677H	December 2020	No evidence	Increased (m) (12, 17)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Theta	P.3	The Philippines	E484K, N501Y, D614G, P681H	January 2021	Increased (m) (9)	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Kappa	B.1.617.1	India	L452R, E484Q, D614G, P681R	December 2020	Increased (v) (18)	Increased (v) (19-22)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.620	Unclear (b)	S477N, E484K, D614G, P681H	February 2021	No evidence	Increased (m) (12, 23)	No evidence	No longer detected or detected

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								at extremely low levels in the EU/EEA
n/a	B.1.617.3	India	L452R, E484Q, D614G, P681R	February 2021	Increased (m) ((9)1)	Increased (m) (12, 14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.214.2	Unclear2	Q414K, N450K, ins214TDR, D614G	December 2020	No evidence	No evidence	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	A.23.1+E484K	United Kingdom	V367F, E484K, Q613H	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								the EU/EEA
n/a	A.27	Unclear (b)	L452R, N501Y, A653V, H655Y	December 2020	Increased (m) (9)	Increased (m) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	A.28	Unclear (b)	E484K, N501T, H655Y	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	C.16	Unclear (b)	L452R, D614G	October 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
n/a	B.1.351+P384L	South Africa	P384L, K417N, E484K, N501Y, D614G, A701V	December 2020	Increased (v) (24)	Increased (v) (25, 26)	Unclear (27)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.351+E516Q	Unclear (b)	K417N, E484K, N501Y, E516Q, D614G, A701V	January 2021	Increased (v) (24)	Increased (v) (25, 26)	Unclear (27)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.1.7+L452R	United Kingdom	L452R, N501Y, D614G, P681H	January 2021	Increased (v) (9)	Increased (m) (14)	Increased (v) (10)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.1.7+S494P	United Kingdom	S494P, N501Y, D614G, P681H	January 2021	Increased (v) (9)	Increased (m) (28)	Increased (v) (10)	No longer detected or detected

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								at extremely low levels in the EU/EEA
Iota	B.1.526	USA	E484K, D614G, A701V	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.526.1	USA	L452R, D614G	October 2020	No evidence	Increased (m) (14)	No evidence	Lineage withdrawn from Pango
n/a	B.1.526.2	USA	S477N, D614G	December 2020	No evidence	No evidence	No evidence	Lineage withdrawn from Pango
Zeta	P.2	Brazil	E484K, D614G	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
n/a	B.1.1.519	Mexico	T478K, D614G	November 2020	No evidence	Increased (m) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	AV.1	United Kingdom	N439K, E484K, D614G, P681H	March 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	AT.1	Russian Federation	E484K, D614G, N679K, ins679GIAL	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	C.36+L452R	Egypt	L452R, D614G, Q677H	December 2020	No evidence	Increased (m) (14)	No evidence	No longer detected or detected

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								at extremely low levels in the EU/EEA
n/a	P.1+P681H	Italy	D614G, E484K, H655Y, K417T, N501Y, P681H	February 2021	No evidence	Unclear (29, 30)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Mu	B.1.621	Colombia	R346K, E484K, N501Y, D614G, P681H	January 2021	Increased (m) (9)	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Lambda	C.37	Peru	L452Q, F490S, D614G	December 2020	No evidence	Increased (v) (31, 32)	No evidence	No longer detected or detected at extremely low levels in

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								the EU/EEA
n/a	AY.4.2	United Kingdom	L452R, T478K, D614G, P681R, A222V, Y145H	June 2021	Increased (v) (33)	Similar (v) (33, 34)	Similar (v) (33)	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	B.1.1.318	Unclear (b)	E484K, D614G, P681H	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.617.2 + K417N	United Kingdom	L452R, T478K, D614G, P681R, K417N	June 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	C.1.2	South Africa	D614G, E484K, H655Y, N501Y,	June 2021	Increased (m) (9)	Increased (m) (12)	No evidence	No longer detected or

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
			N679K, Y449H					detected at extremely low levels in the EU/EEA
n/a	B.1.617.2 + E484X (d)	India	L452R, T478K, D614G, P681R, E484X (d)	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	B.1.617.2 + Q613H	India	L452R, T478K, D614G, P681R, Q613H	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	B.1.617.2 + Q677H	India	L452R, T478K, D614G, P681R, Q677H	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Beta	B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V	September 2020	Increased (v) (24)	Increased (v) (25, 26)	Increased (v) (11, 27)	No longer detected or detected at extremely low levels in the EU/EEA
Gamma	P.1	Brazil	K417T, E484K, N501Y, D614G, H655Y	December 2020	Increased (v) (35)	Increased (v) (36)	Increased (v) (11)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.640	The Republic of Congo	D614G, F490R, N394S, N501Y, P681H, R346S, Y449N, 137−145de	September 2021	No evidence	No evidence	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	XF	United Kingdom	Omicron-like	January 2022	No evidence	No evidence	No evidence	No longer detected.

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
n/a	XD	France	NTD Delta-like; remaining Omicron-like	January 2022	No evidence	No evidence	No evidence	No longer detected.
Delta	B.1.617.2	India	L452R, T478K, D614G, P681R	December 2020	Increased (v) (37)	Increased (v) (38-40)	Increased (v) (39, 41)	Detected at extremely low levels in the EU/EEA
Omicron	BA.1	South Africa and Botswana	(x)	November 2021	Increased (v) (42, 43)	Increased (v)(44-46)	Reduced (v) (47-49)	Detected at extremely low levels in the EU/EEA
Omicron	BA.3	South Africa	(z)	November 2021	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	BA.2 + L452X	n/a	L452X	n/a	No evidence	Increased (50)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XAK	Germany		June 2022	No evidence	No evidence	No evidence	No longer detected.

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Omicron	B.1.1.529 + R346X	n/a	R346X	n/a	No evidence	No evidence	No evidence	Instead of mutational proxies, tracking by lineages (majorly BQ.1 and BF.7)
Omicron	B.1.1.529 + K444X, N460X	n/a	K444X, N460X	n/a	No evidence	Increased (m)(51)	No evidence	Instead of mutational proxies, tracking by lineages (majorly BQ.1)
Omicron	B.1.1.529 + N460X, F490X	n/a	N460X, F490X	n/a	No evidence	Increased (m)(51)	No evidence	Instead of mutational proxies, tracking by lineages (majorly BA.2.75 and XBB)
Omicron	BA.2.3.20	n/a	K444R, L452M, N460K	n/a	No evidence	No evidence	No evidence	Detected at extremely low

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								levels in the EU/EEA
Omicron	BF.7	n/a	R346T, F486V	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	BA.2	South Africa	(y)	November 2021	Increased (v)(42, 52)	Increased (v) (46)	Reduced (v)(53, 54)	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	BA.4	South Africa	L452R, F486V, R493Q	January 2022	No evidence	Increased(50, 55)	No evidence	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Omicron	BA.5	South Africa	L452R, F486V, R493Q	February 2022	No evidence	Increased(50, 55)	Unclear (56)	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	XBC (x)	n/a	N440K, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BN.1	n/a	R346T, K356T, F490S,	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	XAY	n/a	F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BQ.1	n/a	K444T, N460K	n/a	Increased (5)	Increased (2, 3, 61-63)	Unclear (64)	Detected at extremely low levels in the EU/EEA
Omicron	XBB (z)	n/a	N460K, F490S	n/a	Increased (1)	Increased(57-61)	Unclear(62)	Detected at extremely low levels in the EU/EEA

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Omicron	CH.1.1	n/a	K444T, L452R	n/a	Increased (1, 63)	Increased (v) (57, 58, 60, 64)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XBB.1.16	n/a	E180V, T478R, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BA.2.75	India	W152R, F157L, I210V, G257S, D339H, G446S, N460K, Q493 (reversion)	May 2022	Unclear (65)	Similar to Baseline (57, 58, 66)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	DV.7.1	n/a	K444T, L452R, L455F	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XBB.1.5-like + L455F + F456L	n/a	**L455F**, **F456L**, N460K, S486P, F490S	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	BA.2.87.1	South Africa	(q) (e)	2023 September	No evidence	No evidence	No evidence	Not detected in EU/EEA

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Omicron	XBB.1.5-like	United States	N460K, S486P, F490S	n/a	Similar to Baseline (1, 2)	Reduced (v) (1, 3, 5)	Similar to Baseline (4)	No longer detected or detected at extremely low levels in the EU/EEA
Omicron	BA.2.86 + R346T + F456L	n/a	R346T, F456L		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA
Omicron	BA.2.86 + R346T	n/a	R346T		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA
Omicron	BA.2.86 + F456L	n/a	F456L		No evidence	No evidence	No evidence	Mutation present in the majority of circulating descendants

Table 3: De-escalated variants.

x: A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, Δ212, ins215EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

y: G142D, N211I, Δ212, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K

z: A67V, Δ69-70, Δ143-145, N211I, Δ212, G339D, S371F, S373P, S375F, D405N, K417N, N440K, G446S, S477N, T478K, E484A,

Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, D796Y, Q954H, N969K
q: G75D,S98F,V126A,W152L,R190S,K417T,K444N,V445G,L452M,N481K,V642G,K679R,S691P,T791I,Y796H,D936G
n/a: not applicable, no WHO label has been assigned to this variant at this time
All sub-lineages of the listed lineages are also included in the variant, e.g., B.1.429.1 is included in B.1.427/B.1.429 as it is a sub-lineage of B.1.429.
(a) No assessment of transmission is given for variants in the monitoring category, only detected/not detected.
(b) The earliest detections from several different countries are close in time and there is no clearly demonstrated travel link to a specific country that explains the detections.
(c) The property of concern for this variant was the fact that there are reports of difficulties associated with detecting it in upper respiratory tract samples. These difficulties were not caused by primer-template mismatch but rather by the virus not being present in sufficient quantities in the upper respiratory tract.
(d) Any amino acid substitution
(e) Preliminary mutations based on a limited number of genomes

Combination Therapy for Immunocompromised Patients

The approach of using a mix of two antiviral drugs alongside monoclonal antibodies seems to be a hopeful and well-tolerated strategy for dealing with prolonged or recurring SARS-CoV-2 infections in at-risk individuals.

Reports show that negative effects like slow heart rate, liver damage and low white blood cell count are seen in fewer than 5% of cases. Nevertheless, the best combination of treatments and how long they should be used is still unclear based on the existing information [3].

Furthermore, the effectiveness of this combination therapy as a first-line treatment for those at higher risk of severe illness or continued viral presence needs further study, especially when compared to single-drug treatments. Prior combinations of antiviral agents and monoclonal antibodies have shown notable effectiveness against earlier strains of the virus.

Update on Clinical Trials about Early Combination Therapy for Vulnerable Patient with New Variants

In patients who are most at risk, the replication of the virus increases the chance of producing SARS-CoV-2 variants that are capable of avoiding neutralization by antibodies. This scenario frequently results in mutations that provide resistance to antiviral treatments, particularly when patients undergo different therapeutic approaches aimed at eliminating the virus. In light of this situation and despite significant support for this treatment approach, professionals are progressively advocating for the implementation of combination therapies. These may involve combining a single antiviral with a monoclonal antibody or employing two antivirals, either with or without the addition of a monoclonal antibody, to treat patients with ongoing infections. However, such recommendations often arise from individual experiences or findings from limited, uncontrolled studies [4]. To date, limited research has been conducted by authors on the methodical application of combination therapies in individuals with compromised immune systems. The majority of these investigations have primarily focused on patients who were already experiencing prolonged or persistent cases of COVID-19 and were mostly hospitalized. For instance, Mikulska and colleagues documented the administration of combination therapy exclusively in hospitalized patients after a median duration of 42 days (IQR 29-100) following SARS-CoV infection, with response rates recorded at 75%, 73% and 82% on day 14, day 30 and at the final follow-up, respectively [5]. D'Abramo and colleagues recently documented the application of combination therapy in a group of 69 patients who were immunosuppressed and hospitalized due to severe COVID-19, with 92 of them requiring oxygen support. The treatment was administered with a median delay of 21 days, with an interquartile range of 8 to 36 days from the onset of symptoms [6]. In this study, the use of monoclonal antibodies (tixagevimab/cilgavimab or sotrovimab) in the antiviral combination was associated with a significantly higher rate of viral clearance [6,7]. In the studies mentioned earlier, the period of viral shedding was found to be longer compared to what we observed in our research; however, the initiation of treatment occurred at a later stage of the infection. Conversely, a recent publication from our team examined the effectiveness and safety of a regimen involving two antiviral medications, with or without the inclusion of a monoclonal antibody. This analysis covered both early treatment (administered within the first ten days after symptom onset) and later treatment (after ten days) in individuals with compromised immune systems. The results revealed that all patients who received early treatment achieved virological clearance by day 30 post-therapy and maintained good health at follow-up. In contrast, the late treatment group showed virological clearance in only 50% of cases, with 75% remaining in good health, while patients receiving late treatment

were more likely to require oxygen (p=0.015), steroid administration (p=0.045) and exhibited increased severity of COVID-19 (p=0.017) [7].

Orth and his team have recently analyzed the largest group of patients thus far, comprising 144 individuals, with 82% of them being immunocompromised. This study examined the effects of combination therapy in relation to specific co-primary endpoints, which included prolonged viral shedding on day 21 post-treatment initiation and the number of days exhibiting a SARS-CoV-2 viral load of 106 copies/ml or more.

The researchers discovered that pre-existing hematological conditions and the commencement of treatment more than five days following diagnosis were significantly linked to an extended duration of viral shedding. This conclusion aligns with our findings, which indicated a notably higher percentage of patients (64%) experienced prolonged infections when antiviral therapy was initiated more than three days after symptom onset. In comparing our data to historical cohorts, we observed a substantial decrease in both mortality rates and the necessity for mechanical ventilation [8].

This comparison was made taking into account observational studies that reported low instances of early antiviral or monoclonal antibody treatments, alongside a mere 4% admission rate to hospitals and a 1.6% rate of persistent infections among immunocompromised patients receiving prompt treatment with N/r alone [9,10].

A recent retrospective analysis conducted by Mazzitelli and colleagues examined the 30-day mortality rates, emergency department access and hospitalization instances among immunocompromised COVID-19 patients treated with either antivirals alone or a combination of antivirals and sotrovimab. The study revealed that there were no notable differences in individual outcome measures between the two treatment groups. However, upon implementing a propensity score weighting method, the researchers found that the combination therapy had a significant positive association with the composite outcome, while altered liver and kidney functions were linked to a negative association. These differing results highlight the necessity for further investigation through new studies focused on comparing monotherapy against combination therapy in immunocompromised individuals [11].

Monoclonal Antibodies for Immunocompromised Population

As of January 2025, Monoclonal Antibodies (mAbs) continue to play a crucial role in managing COVID-19 among immunocompromised patients, who are at increased risk for severe and prolonged illness. These therapies are employed both for pre-exposure prophylaxis and for treatment upon infection.

Pre-Exposure Prophylaxis

Pemivibart (Pemgarda™) is currently the only long-acting monoclonal antibody authorized in the United States for pre-exposure prophylaxis in individuals who are moderately or severely immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination. Administered via intravenous infusion, Pemivibart provides an additional layer of protection for those at high risk. In Europe, Sipavibart (marketed as Kavigale) has been recommended for marketing authorization by the EMA (European Medicines Agency) for prevention of vulnerables Sars-Cov-2 patients aged 12 and older. This recommendation, adopted in December 2024, reflects ongoing efforts to expand prophylactic options for vulnerable populations.

Treatment of Active Infection

The effectiveness of monoclonal antibody treatments can be influenced by the emergence of new SARS-CoV-2 variants, which may evade certain therapies. Consequently, the therapeutic landscape is continually evolving, with new monoclonal antibody combinations being investigated to counteract immune evasion and improve outcomes for immunocompromised patients

1. Early mAb Therapies (Pre-Omicron)

- Bamlanivimab + Etesevimab (Eli Lilly) and Casirivimab + Imdevimab (Regeneron) were early mAb combinations approved for emergency use in COVID-19 treatment.
- These mAbs were highly effective against earlier strains like Alpha and Beta, but their efficacy decreased against variants like Delta and Omicron, due to mutations in the spike protein, which reduced the ability of these mAbs to bind effectively.

2. *Omicron and Beyond*

- Newer mAbs, such as Tixagevimab + Cilgavimab (Evusheld), have shown broader neutralization activity against Omicron and its subvariants. These combinations have become the gold standard for pre-exposure and post-exposure prophylaxis in immunocompromised patients.
- However, Bebtelovimab (Eli Lilly) was an mAb that showed effectiveness against multiple subvariants of Omicron. Despite this, its effectiveness waned with further viral mutations. Other emerging mAb therapies are being designed to target a broader range of variants.

Antiviral Agents for Immunocompromised Patients

Antiviral agents have proven crucial in preventing the replication of SARS-CoV-2 and reducing the viral load in infected individuals. Immunocompromised patients, who often struggle to mount an immune response, benefit significantly from antiviral therapies [12].

1. *Remdesivir*

- Remdesivir, a nucleoside analog, was one of the first antivirals authorized for emergency use during the pandemic. It has been shown to reduce hospitalization time and improve outcomes in hospitalized patients.
- Effectiveness against variants: Remdesivir remains effective against a wide range of variants, making it a staple in COVID-19 treatment. However, it must be administered early in the disease course to maximize its benefit.
  Efficacy: Remains a standard of care for hospitalized patients with moderate to severe COVID-19. In immunocompromised individuals, it helps to reduce viral load and inflammation, particularly in cases requiring hospitalization or oxygen support.
  Considerations: Its use is approved for both outpatient and inpatient settings and it is administered intravenously, typically over a 3-day course.

2. *Paxlovid (Nirmatrelvir + Ritonavir)*

- Paxlovid has emerged as one of the most effective antiviral therapies, especially when administered early in the course of infection. It works by inhibiting the SARS-CoV-2 protease, essential for viral replication.

Efficacy: Continues to be a primary treatment for mild to moderate COVID-19 in immunocompromised patients. This combination works by inhibiting viral replication through protease inhibition and its use has been associated with reduced hospitalization rates and severity.

Considerations: It remains highly effective when administered early (within 5 days of symptom onset) and is often a first-line therapy for outpatient management in this group.

Drug interactions: Caution is required when combining Paxlovid with other medications due to its interaction profile (e.g., corticosteroids, immunosuppressive agents).

- Challenges with Immunocompromised Populations: The combination of nirmatrelvir and ritonavir can interact with certain immunosuppressive drugs, requiring careful monitoring and dose adjustment in patients receiving immunosuppressive therapies.
- Resistance and Variants: Studies have shown that Paxlovid remains effective against most SARS-CoV-2 variants, but the emergence of certain mutations (e.g., in the protease) may pose a challenge for long-term efficacy.

3. *Molnupiravir*

- Molnupiravir is another antiviral option that targets the viral RNA polymerase, leading to errors in the virus's RNA. While it is generally less effective than Paxlovid, it remains a viable option for patients who cannot take Paxlovid due to drug interactions.

Efficacy: It shows moderate benefits in reducing viral replication but is considered a secondary option when other agents are unsuitable.

- *Broad Spectrum:* Molnupiravir has shown some potential to work against various variants, though resistance to the drug could emerge with prolonged use [12].

Triple Combination Therapy: The New Frontiers

As the COVID-19 pandemic continues to change, colleagues are looking into the possibilities of using two antivirals along with monoclonal antibodies for patients with weakened immune systems. The idea behind this approach is that it hits several stages in the virus's life cycle, which can lower the chance of resistance and lead to better treatment results.

Recent studies by Gentile, et al., show that starting combination therapy with sotrovimab and a direct antiviral drug early is safe and may help lower the chances of hospitalization, severe progression of COVID-19 and the risk of prolonged SARS-CoV-2 infection for those with serious immune deficiencies [4].

However, the emergence of new variants could affect the success of this method because of a decrease in the effectiveness of sotrovimab.

Rationale for Triple Therapy

- *Monoclonal Antibodies:* These therapies provide immediate neutralizing effects by binding to the spike protein of the virus, preventing it from entering host cells [14]
- *Antivirals (Remdesivir + Paxlovid):* Remdesivir inhibits viral replication early in infection, while Paxlovid prevents the protease from processing viral proteins necessary for replication
- *Synergistic Effects:* The combination of mAbs with two antiviral agents could provide broad protection against a wider range of variants, especially those with mutations that escape one particular treatment [15]

Clinical Evidence and Ongoing Trials

- Several clinical trials are investigating the safety and efficacy of triple combination therapy. Preliminary results indicate that a combination of Paxlovid + Remdesivir + Evusheld may offer synergistic antiviral and immune-enhancing benefits, especially in immunocompromised patients
- *Early Findings:* Triple therapies may significantly reduce viral loads, accelerate viral clearance and lower the incidence of severe disease in high-risk populations
- *Challenges and Considerations:* Triple combination therapy presents several challenges, including potential drug-drug interactions, cost and accessibility, particularly for resource-limited settings. Close monitoring for adverse effects and drug interactions, particularly in immunocompromised individuals, is crucial [15]

Preclinical and Clinical Evidence for Triple Therapy

- Review studies that have tested combinations of two antivirals (e.g., Remdesivir + Molnupiravir) and monoclonal antibodies (e.g., Casirivimab/Imdevimab)
- Research from major clinical trials, such as ACTIV-3 and RECOVERY, showing positive results from combination therapies
- Data showing improved viral clearance, reduced hospitalization and decreased mortality in immunocompromised patients

Key Considerations for Immunocompromised Patients in 2025

- *Personalized Treatment Plans:* Given the heterogeneity of the immunocompromised population (e.g., cancer therapy patients vs. organ transplant recipients), therapeutic regimens must be highly individualized. This includes adjusting antivirals, monoclonal antibody selection and corticosteroid use based on the patient's immunosuppressive regimen and risk profile
- *Monitoring and Adjusting Therapy:* Immunocompromised patients often have altered drug metabolism and may experience a higher incidence of drug interactions and side effects. Regular monitoring of drug levels, organ function and immune status is vital
- *Evolving Pathogen Variants:* The ongoing emergence of new SARS-CoV-2 variants may impact the effectiveness of available therapies. Regular updates on the performance of antivirals and monoclonal antibodies against new variants are crucial

Challenges and Considerations

- Safety: Risks of drug interactions, toxicity and long-term effects of triple therapies need to be evaluated
- Cost: The financial burden of triple therapies may limit access, especially in low-resource settings
- Variants: Ongoing mutations of the SARS-CoV-2 virus, potentially diminishing the effectiveness of current treatments

Conclusion

Combination therapy has shown a promising impact on overall results, including death rates, hospital stays and emergency room visits among those who are severely immunocompromised and have been vaccinated. The strategy of using two antiviral medications along with monoclonal antibodies appears to be the most effective method, providing a more comprehensive and

sustained response to the evolving SARS-CoV-2 variants. Recent studies suggest that starting combination therapy early, which includes sotrovimab and a direct antiviral drug, may be safe and could help prevent hospitalizations, stop the progression to severe COVID-19 and reduce the likelihood of prolonged SARS-CoV-2 infection in individuals with significant immune system challenges.

Nonetheless, the arrival of new variants might reduce the effectiveness of this method because of a potential loss in the efficacy of sotrovimab. Further investigation is necessary to compare the combined treatment with single-drug therapy in these patient groups, especially considering the reduced effectiveness of the monoclonal antibody.

Conflict of Interest
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Author's Contribution
The authors contributed equally.

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