

# Expert consensus on combination antiviral therapy for high-risk COVID-19 patients: A timely call to action

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**SUMMARY:** On May 5, 2023, the WHO declared that the COVID-19 pandemic no longer constitutes a public health emergency of international concern (PHEIC), but SARS-CoV-2 continues to spread and evolve on a global scale. The WHO reported that COVID-19 still poses a threat to humanity, and especially in some areas with large numbers of infected people. For some high-risk COVID-19 patients, such as those with underlying conditions, elderly patients, patients who need long-term immunosuppressive therapy after organ transplantation, patients with immunosuppressive diseases, patients who tend not to test negative for SARS-CoV-2 despite standard antiviral therapy, and cancer patients, special attention is still required after infection with SARS-CoV-2. How to clear SARS-CoV-2 in a timely manner is the key to treating such patients. Based on the demands of clinical practice and medical evidence, the National Center for Infectious Diseases of China assembled experts from relevant disciplines to reach the Chinese expert consensus on the combined use of antivirals to treat COVID-19, providing timely suggestions to resolve the medication issues that have been plaguing clinical practice. The consensus suggests that for special patients, combined medication can promptly eliminate the virus without increasing the risk to patient safety.

**Keywords:** SARS-CoV-2, COVID-19, special patients, antiviral therapy, small-molecule drugs, drug combination, expert consensus

## 1. Introduction

On May 5, 2023, the WHO declared that the COVID-19 pandemic no longer constitutes a public health emergency of international concern (PHEIC). Significant progress has been made in the global response to the COVID-19 pandemic, but SARS-CoV-2 continues to spread and evolve on a global scale. The continuous mutation of SARS-CoV-2 means that it continues to threaten human health and that it also hampers existing antiviral treatment strategies. The WHO emphasizes that all countries must continue to implement prevention and control measures, including monitoring virus mutations, enhancing vaccination for high-risk groups, and optimizing clinical capabilities, to consolidate the achievements made in the prevention and control of this epidemic.

A large number of COVID-19 patients are still seen in clinical practice. Some high-risk COVID-19 patients, such as those with underlying conditions, elderly patients, patients who need long-term immunosuppressive therapy after organ transplantation, patients with immunosuppressive diseases, patients who tend not to test negative for SARS-CoV-2 despite standard antiviral

therapy, and cancer patients, are prone to develop severe or even critical COVID-19, making clinical treatment relatively challenging. This is why the National Center for Infectious Diseases of China assembled experts from relevant disciplines into a team. The team conducted a systematic literature search, identified key issues, put forward relevant recommendations, and reached the Chinese expert consensus on the combined use of antiviral drugs for novel coronavirus infection (1), providing timely suggestions to resolve the medication problems that have been plaguing clinical practice.

## 2. There is still a large number of COVID-19 patients, with some requiring hospitalization and a few deaths related to the virus

According to the official website of the WHO, in the 28 days from June 30 to July 27, 2025, a total of 80,765 new cases were reported in 90 countries across five of the WHO's regions. Overall, new cases from 27 countries in Africa, the Americas, Europe, and Southeast Asia increased by more than 10%. During this period, 171 new ICU hospitalizations were reported in 32 countries

across four of the WHO's regions. Of the 31 countries that have continued to report hospitalized cases over the past 28 days, 10 countries in the Americas, Europe, and the Western Pacific have reported an increase in cases. Of the 24 countries that continued to report ICU admissions during the same period, 4 countries in the Americas and Europe have reported an increase in cases. During that period, 41 countries in five of the WHO's regions reported a total of 846 new COVID-19 deaths. The number of new deaths in 9 countries in the Americas, Europe, and Southeast Asia has increased by more than 10%. In June 2025, 87% of the cases of death reported

with information on age occurred involved individuals age 65 and older (2).

As of July 27, 2025, a total of 778,457,848 cases of COVID-19 have been reported worldwide. This does not include cases in some countries that have stopped extensive monitoring of COVID-19 cases and cases that have not been reported to the WHO. As of July 27, 2025, a total of 7,099,375 deaths related to COVID-19 have been reported worldwide. In the past week, from July 21 to July 27, 2025, 166 new deaths were reported (2). According to a WHO report, COVID-19 still poses a threat to humanity, and especially in some areas (Figures 1 and 2).

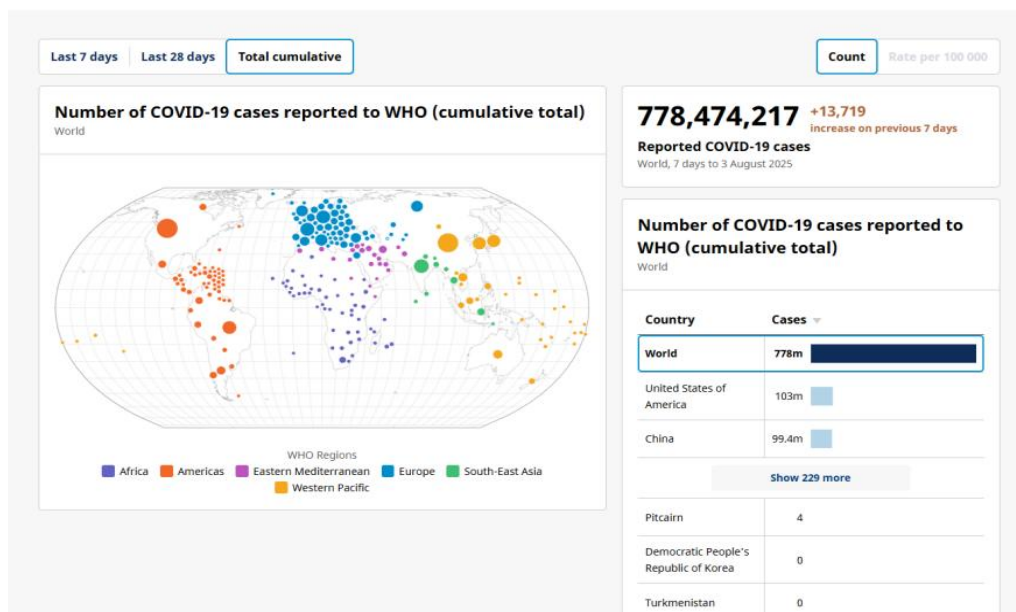


Figure 1. Number of COVID-19 cases reported to the WHO (cumulative total), as of August 3, 2025 (Source: World Health Organization, WHO COVID-19 Dashboard).

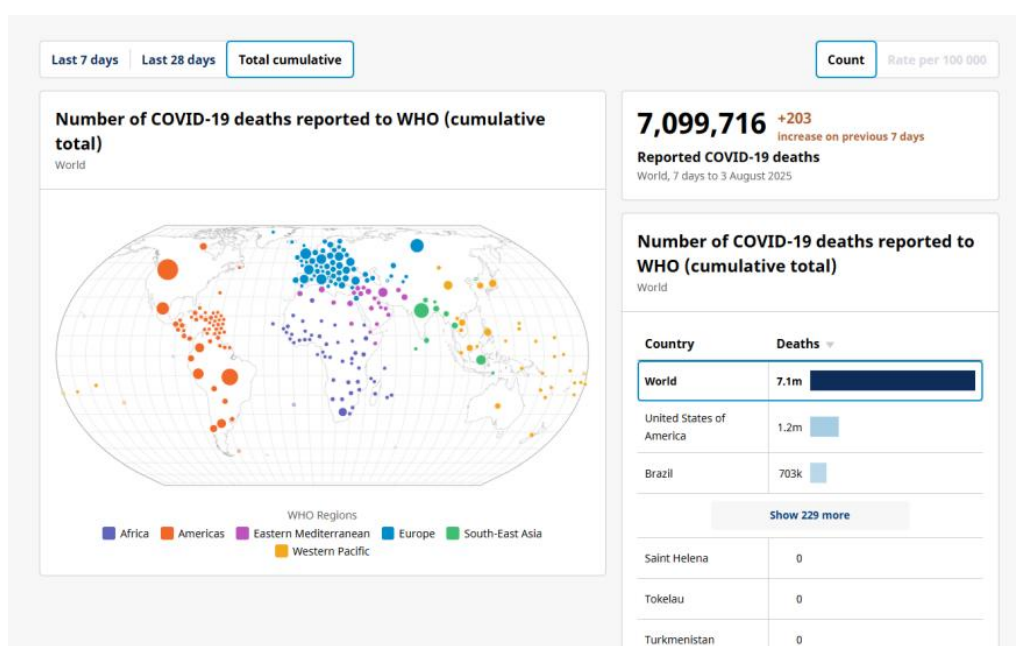


Figure 2. Number of COVID-19 deaths reported to the WHO (cumulative total), as of August 3, 2025 (Source: World Health Organization, WHO COVID-19 Dashboard).

According to surveillance data from sentinel hospitals of the Chinese Center for Disease Control and Prevention, the number of COVID-19 patients in China has currently increased significantly compared to before. SARS-CoV-2 is now the most common respiratory pathogen among all common respiratory pathogens. In both southern and northern provinces and cities, COVID-19 is most often detected in outpatient influenza-like cases. The continuous spread of the virus, and especially among high-risk groups with weakened immunity (such as the elderly and those with underlying conditions), makes effective antiviral treatment plans particularly crucial.

From January 10, 2020 to August 18, 2025, Shenzhen Third People's Hospital, which is a designated hospital for COVID-19 treatment, treated 52,478 outpatients and emergency patients with COVID-19 and admitted 14,533 patients. From May 5, 2023 to August 18, 2025, that is, after the WHO declared that the COVID-19 pandemic no longer constituted a public health emergency of international concern, Shenzhen Third People's Hospital treated 15,906 outpatients and emergency patients with COVID-19 and admitted 2,536 patients. Except for a few patients, the vast majority needed to be hospitalized due to underlying conditions such as diabetes, hypertension, cardiovascular and cerebrovascular diseases, chronic kidney disease, AIDS, and post-organ transplantation. However, infection with SARS-CoV-2 has aggravated underlying conditions in a considerable number of patients.

### **3. In the post-COVID era, attention still needs to be paid to the characteristics of the COVID-19 pandemic, and especially the evolution and mutation of SARS-CoV-2, as well as to research and development of COVID-19 vaccines and new drugs**

At present, a considerable amount of experience has been gained in the diagnosis and treatment of COVID-19 patients. However, there are still several aspects that need attention. (i) There are many patients with long COVID, which hampers their work and life. According to conservative estimates, at least 400 million people worldwide who have been infected with SARS-CoV-2 also have "long COVID" (3). Long COVID symptoms can cover multiple systems, including the respiratory, nervous, urinary, reproductive, motor, digestive, endocrine, and immune systems, and range from mild to severe (4-7). However, the mechanism of long COVID remains unclear. (ii) Some patients, such as those age 60 or older and HIV patients with other diseases, have a higher risk of death after infection with SARS-CoV-2 (8). In addition, patients with underlying conditions, elderly patients, patients who need long-term immunosuppressive therapy after organ transplantation, patients with immunosuppressive diseases, patients who tend not to test negative for

SARS-CoV-2 despite standard antiviral therapy, and cancer patients, are prone to develop severe or even critical COVID-19 after infection with SARS-CoV-2, and their clinical treatment is relatively difficult. (iii) COVID-19 is significantly associated with an increased risk of developing other diseases, such as diabetes. Close monitoring of blood glucose should be considered after contracting COVID-19, and especially for adult patients who require hospitalization or ICU admission (9). (iv) Cancer patients are a group that is highly vulnerable to COVID-19. Due to immunosuppression caused by the malignant tumor itself or anti-cancer treatment, cancer patients have a poor prognosis (10). (v) At present, many countries are at a standstill in the research and development of COVID-19 vaccines and drugs and do not view them as crucial. A study has found that the effectiveness of preventing COVID-19 may increase with an increase in vaccination (11). (vi) The evolution of SARS-CoV-2 is related to vaccination and other factors. Now that the pandemic has ended, the global vaccination rate has declined, both for the general population and for those most likely to develop severe illness from the virus. This indicates that the efficacy of the vaccine may be diminishing. Detection and sequencing of SARS-CoV-2 is also decreasing. Moreover, the process of tracking viruses has become increasingly complex, thereby providing a selective advantage for SARS-CoV-2 and enabling it to evolve quietly (12).

In current clinical practice, however, the resistance of SARS-CoV-2 to antivirals, the rebound of viral load after treatment with certain drugs (such as Paxlovid), and the urgent need for rapid virus clearance in the treatment of critically ill patients all suggest that existing single-agent treatment regimens may have limitations in some cases, and the potency of their inhibition may be insufficient. Therefore, exploring the combined use of antivirals with different mechanisms of action to achieve better efficacy has become an important research direction.

Researchers have discovered multiple SARS-CoV-2 variants, including Alpha, Beta, Gamma, Delta, and Omicron. These variants differ in terms of transmissibility and pathogenicity, with the Omicron variant having greater immune escape ability. The rapid emergence of virus variants not only poses challenges to the efficacy of vaccines and existing prevention and control strategies but may also affect the effectiveness of single-agent antiviral therapy and increase the risk of drug resistance, thereby further highlighting the urgency of exploring more robust treatment strategies such as combination therapy.

### **4. After conventional single medications treatment and regular courses of treatment, the virus in some special patients still has difficulty turning negative. Combined medication can help eliminate the virus as soon as possible and increase the success rate of rescue**

For COVID-19 patients, routine diagnosis and treatment should be based on the COVID-19 Diagnosis and Treatment Protocol (draft Version 10) issued by the National Health Commission of China and relevant prescription information. Nirmatrelvir and ritonavir should be used for 5 days, or molnupiravir for 5 days, or azvudine for up to 14 days. Monotherapy is recommended (13). In clinical practice, however, patients who have not tested negative for viral nucleic acids despite treatment with a single antiviral are often encountered, and especially the elderly with multiple underlying conditions, patients who have been using immunosuppressants for a long time after organ transplantation, and patients with immune deficiencies. A clinical study in China examined COVID-19 patients with relatively mild symptoms. A total of 1,571 hospitalized COVID-19 patients were included in this retrospective cohort study. Of them, 272 received nirmatrelvir-ritonavir and 156 received azvudine. Results indicated that the 28-day negative nucleic acid conversion rate was 216/272 (79.41%) in the nirmatrelvir-ritonavir group and 132/156 (84.62) in the azvudine group (14). In other words, even among patients with relatively mild COVID-19 symptoms, about 20% who receive single antiviral therapy tend not to test negative for viral nucleic acids.

#### **5. Similar to the cocktail therapy for AIDS, antivirals with different pharmacological mechanisms of action should be used to promptly eliminate the virus without increasing adverse drug reactions**

From a pharmacological perspective, the combined use of antivirals with different mechanisms of action, as exemplified by the cocktail therapy used to fight AIDS, is a common strategy to enhance efficacy and reduce the risk of drug resistance. This theory is also applicable to the treatment of COVID-19. At present, the oral small-molecule antivirals mainly used in clinical practice can be roughly classified into two categories: 3CL protease inhibitors as exemplified by nirmatrelvir/ritonavir, simnetelvir/ritonavir (Xiannuoxin), and leritrelvir, and RNA-dependent RNA polymerase (RdRp) inhibitors as exemplified by molnupiravir, azvudine and VV116, which act by inhibiting different stages of viral replication. Cases encountered in clinical practice and various studies have also confirmed the feasibility and potential advantages of this combined strategy, and especially when treating patients with weakened immune function or complex conditions.

#### **6. Combination therapy for some special patients has been successful**

A study collected data on nearly 10,000 patients who had received antivirals for COVID-19 in 8 domestic hospitals in China, and it analyzed the changes in viral load after taking the drugs (15). Results indicated that combining

antivirals with different mechanisms of action was better at inhibiting SARS-CoV-2. Case series studies have also indicated that for some special patients, such as those who are critically ill, immunosuppressed, post-transplant, or who tend not to test negative for viral nucleic acids after conventional treatment, combined use of small-molecule antivirals can, when virus clearance is the main goal, significantly increase the rate at which nucleic acids are detected. It helps to eliminate the virus as soon as possible, improve the success rate of rescue, and does not increase safety risks (16).

#### **7. An expert consensus provides new ideas and suggestions regarding antiviral therapy for special patients**

Based on the demands of clinical practice and medical evidence, the National Center for Infectious Diseases of China assembled experts from disciplines such as infectious diseases, respiratory internal medicine, critical care medicine, and clinical pharmacy to form a team. The team conducted a systematic literature search, identified key issues, and put forward relevant recommendations, reaching the Chinese expert consensus on the combined use of antiviral drugs for novel coronavirus infection (1) in order to provide a reference for clinical practice. A point worth noting is that the expert consensus suggests that for patients with confirmed COVID-19, the routine use of a single drug should be considered first. In some high-risk COVID-19 patients where virus clearance is still the main goal, the combined use of small-molecule antivirals can help to clear the virus as soon as possible and improve the success rate of rescue.

#### **8. Conclusion**

There are still many patients with COVID-19, and sufficient attention still needs to be paid to the COVID-19 epidemic. Clinical practice and numerous sources have confirmed that for special patients, combined medication can promptly eliminate the virus without increasing the risk of drug safety. The publication of the Chinese expert consensus on the combined use of antivirals to treat COVID-19 provides timely suggestions to resolve the medication problems that have long plagued clinical practice. Continuous monitoring should be enhanced and the SARS-CoV-2 genome should be analyzed and determined in light of complex and volatile trends in current viral epidemics to enable the issuance of more timely warnings, targeted response measures should be implemented, and relevant drug and vaccine research and development should be carried out.

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