CORONAVIRUS INFECTIONS DRUGS FOR THEIR TREATMENT

VI term
Lesson 13

QUESTIONS FOR THE LESSON

1. Characteristics of the Coronaviridae family. Classification.
2. The structure of the coronavirus virion.
3. RSV life cycle.
4. Therapy of coronavirus infections:
Dexamethasone, Remdesivir, Favipiravir.

CHARACTERISTICS OF THE CORONAVIRUS FAMILY

Coronaviridae is a family of viruses that includes two subfamilies: Coronavirinae and Torovirinae. Pathogens important to humans belong to the subfamily Coronavirinae.

Human coronaviruses (Hcov) were first identified in the 60s of the last century: HCoV-OC43 (OC43) and HCoV-229E (229E). Later, other human coronaviruses were detected: HCoV-NL63 (NL63) in 2004 and HCoV-HKU1 (HKU1) in 2005. These viruses are not considered to be the main causative agents of diseases of the upper and lower respiratory tract, including in the elderly, immunocompromised patients, and infants. These four viruses usually cause acute diseases of the upper and lower respiratory tract. The severe course of these diseases is rarely recorded. As a rule, this is due to concomitant pathology and/or immunological aging.

However, over the past 15 years, two new human coronaviruses have emerged that cause significant morbidity and mortality. Severe acute respiratory syndrome (SARS) was identified in 2003. SARS-CoV causes acute, atypical pneumonia and diffuse alveolar lesion, which has been reported in approximately 8,000 patients.

People over the age of 65 often develop acute respiratory distress syndrome, resulting in a mortality rate in this group of patients exceeding 50%. Overall, SARS-CoV infection, called "SARS", caused the deaths of 774 people, i.e. about 10% (see Figure 1). Most recently, in 2012, a new human coronavirus, Middle East respiratory syndrome coronavirus (MERS–CoV), was identified (see Figure 2) 1,728 cases of MERS have been reported, and the disease has caused 622 deaths, accounting for approximately 36% of deaths. Just as in the case of SARS, MERS is particularly severe in patients over 65 years of age and patients with concomitant diseases.

Figure 1. Global spread of SARS. The number of reported SARS cases and the date of the first identified case in each country (group of countries) are indicated. The countries marked in red are those countries where significant local transmission has occurred. (http://www.who.int/csr/sars/country/table2004_04_21/en/).

Figure 2. Global distribution map of MERS-CoV.
(http://www.who.int/csr/disease/coronavirus_infections/risk-assessment-7july2015/en/).

SARS-CoV and MERS-CoV have a clearly proven zoonotic origin, although their exact pathways from the animal reservoir to the human infection are not yet clear. SARS-CoV viruses with high nucleotide identity were found in coronoviruses isolated from palm martens and raccoon dogs in the Chinese province of Guangdong during the SARS epidemic of 2002-2003. More recent studies have identified highly conserved variants of coronaviruses circulating in bat populations, including several strains that are capable of infecting human cells. MERS-CoV has caused sporadic infections, along with several local outbreaks throughout the Middle East since its discovery in 2012. Although much remains unknown, closely related viruses have been isolated from camels and highly affinity coronavirus variants from the African bat Neoromicia capensis.

Coronaviruses belong to one of the two subfamilies Coronaviridae and Torovirinae in the family Coronaviridae, which, in turn, belong to the order Nidovirales (Figure 3).

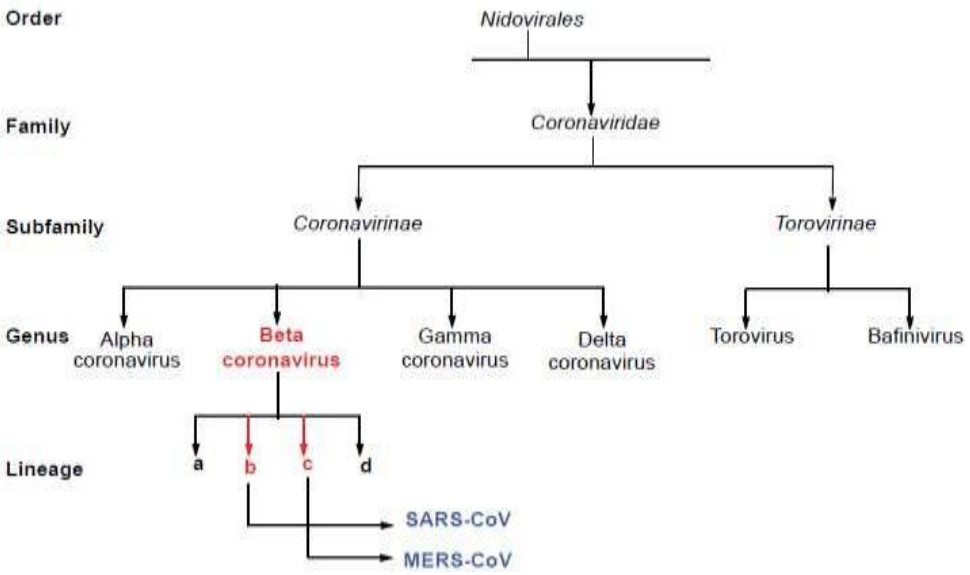
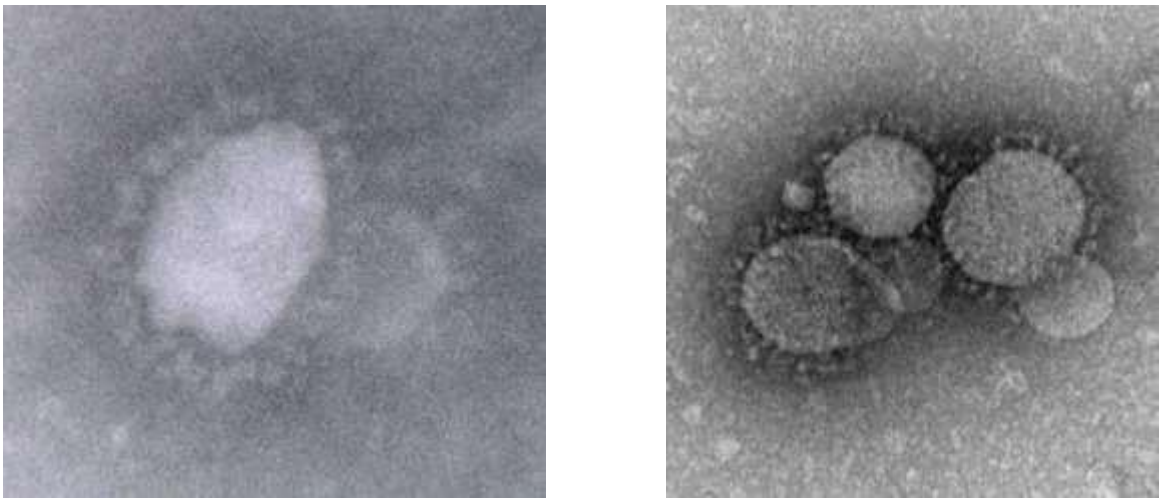


Figure 3. Schematic representation of the Coronaviridae taxonomy (according to the International Committee on the Taxonomy of Viruses). SARS-CoV and MERS-CoV belong to the genus Betacoronavirus, but they have different lineages.

VIRION STRUCTURE AND THE RSV REPLICATIVE CYCLE

- The virion of coronaviruses has SARS-CoV and MERS-CoV spherical shape, with a diameter of about 120 nm (see Figure 4).
- The virion has a lipid membrane that contains a "spike" glycoprotein S in the form of a trimer and hemagglutinin-esterase glycoprotein NOT in the form of a dimer.

- Viruses of this family are characterized by the presence of glycoproteins on the outer shell that expand towards the distal end, which resembles the solar corona during an eclipse. Hence the name of the family.



SARS-CoV MERS-CoV

Figure 4. Electronic photographs of SARS-CoV and MERS-CoV virions.

- In addition to glycoproteins, the membrane contains other proteins: membrane protein M and small membrane protein E, which forms a homopentomer.
- Genomic RNA is associated with protein N, which forms a capsid (nucleoprotein) and performs protective functions. The capsid shape of viruses of the Coronavirinae subfamily is circular, while viruses of the Torovirinae subfamily are tubular.

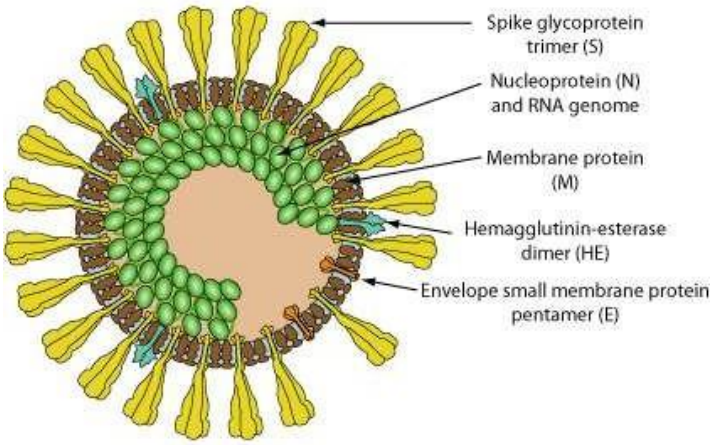


Рисунок 4. Строение вириона коронавирусов.

– The coronavirus genome is represented by linear single-stranded RNA of positive polarity. The volume of the genome is 27-32 kb and is the largest genome of all currently known RNA virus genomes.

LIFE CYCLE:

- Coronaviruses bind to cells on the surface of which there are receptors containing N-acetylneuramic acid, which belongs to the group of sialic acids.
- Glycoprotein HE binds to N-acetylneuramic acid, which has neuraminase activity.
- The spike glycoprotein S then binds to the cellular receptor ACE2 (SARS-CoV) or DPP4 (MERS-CoV).
- Then, through endocytosis and subsequent fusion of the viral and cell membranes, viral RNA enters the cytoplasm of the cell. Since the genomic RNA of coronaviruses has a positive polarity, it is used both as mRNA and for replication, first into anti-genomic, and then based on anti-genomic into genomic RNA.
- The maturation of viral proteins S, E, HE, and M begins on the membrane of the endoplasmic reticulum and the Golgi apparatus.
- The processing of structural and non-structural proteins proceeds in parallel. Protein N binds to a copy of the genomic RNA and forms a nucleoprotein;
- This nucleoprotein is transported to the membrane of the Golgi apparatus, where it binds to viral glycoproteins.
- Mature virions bud off inside a vesicle, in which they are then transported to the cell surface (see Fig. 5).

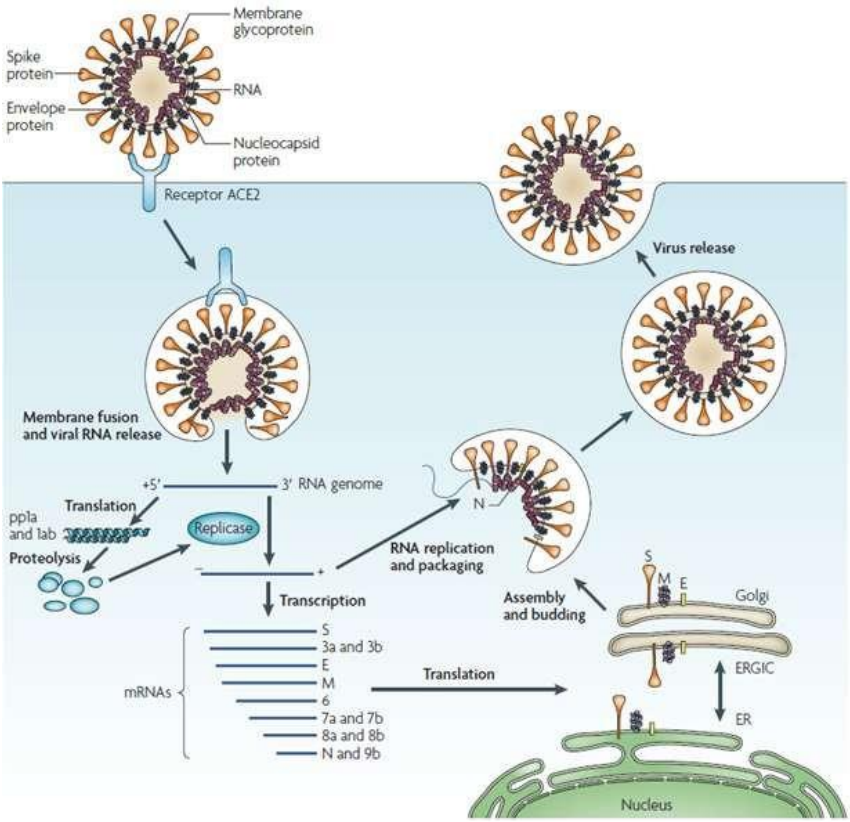


Figure 5. Life cycle diagram of SARS-CoV and MERS-CoV.

ТЕРАПИЯ КОРОНАВИРУСНЫХ ИНФЕКЦИЙ

Currently, there is no adequate treatment. There are a number of factors that seriously hinder the search for effective blockers of coronavirus replication. First of all, it is quite difficult to assess the contribution of coronaviruses to the development of a particular form of pathology, since diseases are combined with secondary bacterial infections. In addition, human coronaviruses are difficult to grow in the laboratory. It takes time to overcome this problem, which is related to the selection of optimal conditions and the creation of an adequate cellular model. As a result, the life cycle of human coronaviruses has not been well studied, and the details and specificity of the interaction between the virus and the host cell, as well as the functioning of viral enzymes, remain unclear. This could not but affect the achievements in the search for anti-coronavirus drugs.

SARS-CoV-2 leads to a large release of cytokines, causing a strong immune response. The immune response is one of the causes of acute lung injury and acute respiratory distress syndrome. At the beginning of the pandemic, China used corticosteroids, but WHO did not recommend their use due to lack of evidence of possible effectiveness, while the Chinese medical team appealed, arguing that small doses help reduce mortality.

The researchers found that a number of drugs inhibit proteases.

— viral enzymes that play a leading role in viral replication. Previous work has shown that two coronavirus proteases, Mpro and PLpro— are convenient targets for potential antiviral drugs. Paxlovid, developed by Pfizer for the treatment of COVID-19, is aimed at Mpro. Both enzymes are relatively stable, meaning they rarely undergo mutations, so it is unlikely that the coronavirus will quickly develop drug resistance to such therapy.

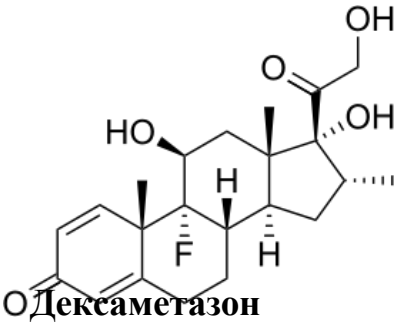
SARS-CoV-2 produces proteins called polyproteins, which are encoded by the RNA genome. These long molecules must be cleaved by proteases into individual proteins, which leads to the formation of functional viral enzymes and proteins capable of starting viral replication.

In the course of the study, scientists analyzed 64 compounds, including inhibitors of HIV and hepatitis C proteases, cysteine proteases (found in protozoa) and dipeptidyl peptidase, an enzyme involved in the development of type 2 diabetes. 11 molecules (including MG-101, lycorin, and nelfinavir mesylate) have been identified to affect Mpro activity, and five (for example, sitagliptin and daclatasvir) have been identified to affect Plpro.

Experiments on human cell cultures have shown that eight of the sixteen drugs had dose-dependent antiviral activity by inhibiting proteases. At the same time, only MG-101 affected the penetration of the virus into cells..

DEXAMETHASONE

According to the preliminary results of a study conducted in the UK, dexamethasone helps to reduce the mortality of patients on mechanical ventilation by a third, and by a fifth among patients who require oxygen therapy. A meta-analysis and systematic review of COVID-19 treatment with various drugs shows that glucocorticosteroids probably still reduce mortality and the risk of mechanical ventilation among patients compared with conventional patient care.



Дексаметазон

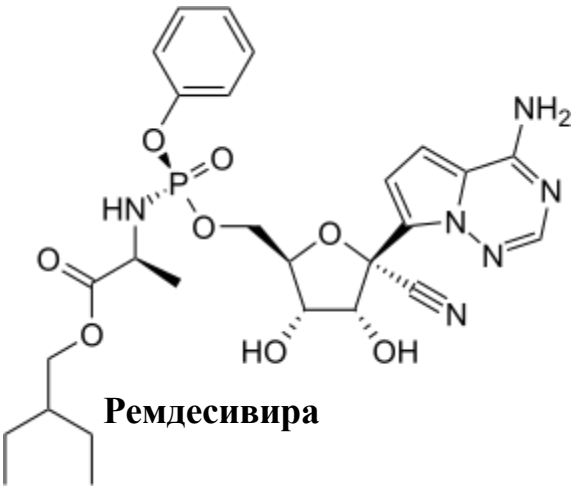
Although unlicensed drugs and experimental therapies are used in practice, such treatment should take place within the framework of ethically sound clinical trials. Case series studies may be biased, which may create a false sense of the safety and effectiveness of experimental therapies. Conducted research must be of high quality, poor research quality leads to a waste of resources and, by definition, is not ethical. The use of drugs with unproven efficacy can harm critically ill patients. For example, chloroquine, hydroxychloroquine, azithromycin, as well as lopinavir and ritonavir are associated with a potential increased risk of death due to heart problems.

Therapy appointments should be based not on hypotheses, but on clinical studies confirming the effectiveness. Hypotheses can be the basis for conducting a planned clinical trial. WHO considers it ethically acceptable to use experimental therapies individually outside of clinical trials in connection with an emergency situation, if the patient has been informed and has given his consent. Such therapies should be supervised, and the results should be documented and made available to the scientific and medical community.

Chloroquine, hydroxychloroquine, azithromycin, lopinavir and ritonavir have no advantages over standard treatment (maintenance therapy) either in monotherapy or in combination with umifenovir or interferons, while significantly increasing the risk of side effects.

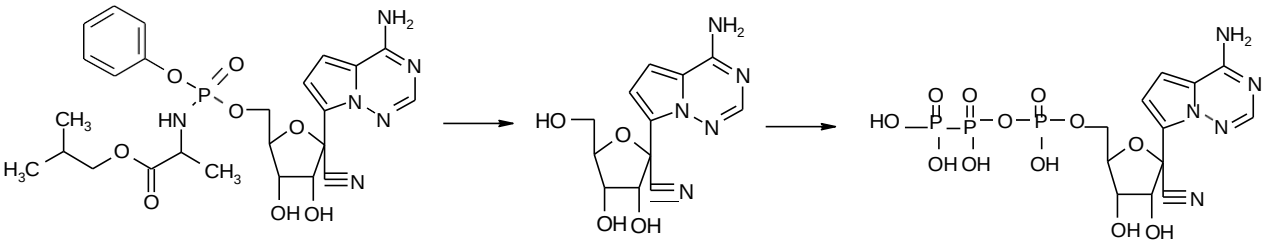
REMDESIVIR

Remdesivir, a drug developed against the Ebola virus, has been found to have antiviral activity against SARS-CoV-2 in the laboratory. The positive results of the early studies attracted the attention of the media and led to the initiation of emergency use of the drug. However, remdesivir has little effect on all-cause mortality for up to 28 days in hospitalized adults with SARS-CoV-2 infection.



Ремдесивира

Remdesivir is a direct-acting antiviral drug that inhibits the RNA-dependent RNA polymerase of the virus. As an analog of adenosine, nucleoside triphosphates (GS-443902), the active metabolite of remdesivir, interferes with the action of viral RNA-dependent RNA polymerase and eludes viral exoribonuclease (ExoN) testing, causing a decrease in viral RNA production. In some viruses, such as respiratory syncytial virus, it causes RNA-dependent RNA polymerase to stop, but its predominant effect (as in the case of the Ebola virus) is irreversible chain termination.



Unlike many other chain terminators, this is not mediated by preventing the addition of the immediately following nucleotide, but instead occurs with a delay occurring after the addition of five additional bases to the growing RNA chain. For the RNA-dependent RNA polymerase MERS-CoV, SARS-CoV-1 and SARS-CoV-2, RNA synthesis stops after the inclusion of three additional nucleotides.

In November 2020, the World Health Organization (WHO) updated its COVID-19 treatment guidelines to include a conditional recommendation against the use of remdesivir based on the results of the WHO Solidarity study. The European Medicines Agency has announced that they will evaluate the new data to see if a review of the remdesivir approval is required.

In the European Union, remdesivir is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged twelve years and older with a body weight of at least 40 kg (88 lb)) with pneumonia requiring additional oxygen.

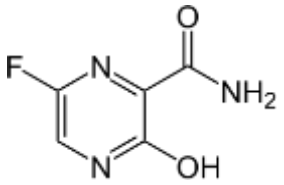
Nevertheless, remdesivir, despite the rather weak evidence of its effectiveness and high cost, is currently part of the standard treatment packages in some countries. Remdesivir was the first among all drugs to receive full approval from the FDA (USA) for use in the treatment of people over 12 years of age and weighing at least 40 kilograms who require hospitalization due to coronavirus infection.

FAVIPIRAVIR

6-fluoro-3-hydroxypyrazine-2-carboxamide

Favipiravir has been studied as a potential treatment for COVID-19 since February 2020.

In a study on evidence-based medicine standards completed in Japan in 2020, no significant effect of favipiravir in the treatment of COVID-19 was found.

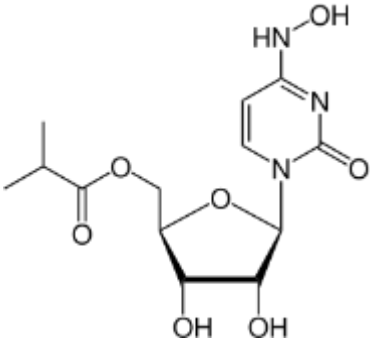


Favipiravir

As of August 2021, favipiravir has no evidence of efficacy in terms of reducing Favipiravir mortality and ventilator risk. As of November 2021, favipiravir does not accelerate the recovery of COVID-19 patients. The Canadian biotech company that conducted the study found it futile against COVID-19. In the vast majority of countries around the world, favipiravir is not used to treat COVID-1.

MOLNUPIRAVIR

((2R,3S,4R,5R)-3,4-dihydroxy-5-(4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)- yl)tetrahydrofuran-2-yl)methyl isobutyrate



Molnupiravir (development codes MK-4482 and EIDD- 2801) is an antiviral drug that is active when taken orally. It suppresses the replication of certain RNA viruses. It is used for treatment COVID-19 in people infected with SARS-CoV-2.

This is about a drug based on a synthetic nucleoside derivative of N4-hydroxycytidine

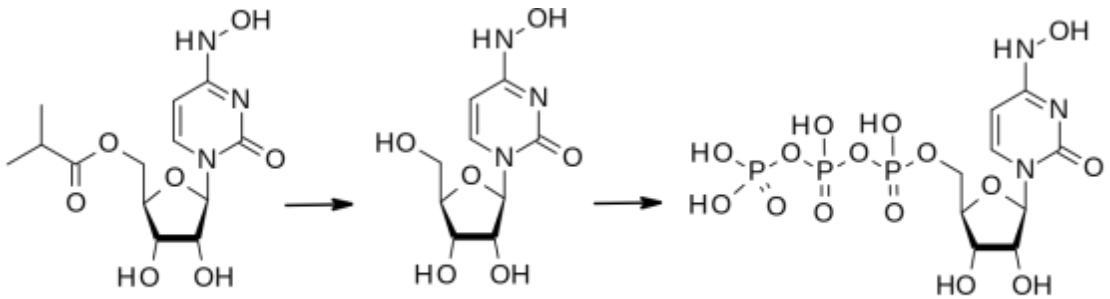
(also known as EIDD-1931) exerts its antiviral effect by introducing copying errors during viral RNA replication.

The drug was developed for the treatment of influenza at Emory University by the university pharmaceutical company Drug Innovation Ventures at Emory (DRIVE). It was then acquired by Miami-based Ridgeback Biotherapeutics, which later entered into an agreement with Merck & Co. to further develop the drug.

On November 4, 2021, the United Kingdom became the first country to approve the use of molnupiravir for the treatment of COVID-19.

Mechanism of action

Molnupiravir suppresses viral reproduction by promoting the spread of mutations during viral RNA replication using RNA-directed RNA polymerase. It is metabolized into a cytidine-like ribonucleoside analog, β-D-N 4-hydroxycytidine 5'-triphosphate (also known as 5'-triphosphate EIDD-1931 or NHC-TP). During replication, the viral enzyme includes NHCTP in the newly created RNA instead of using real cytidine.



Molnupiravir metabolism.svg

Molnupiravir can switch between two forms (tautomers), one of which mimics cytidine (C) and the other uridine (U). NHC-TP is not recognized as an error by exonuclease enzymes that can replace mutant nucleotides with corrected versions.When viral RNA polymerase tries to copy RNA containing molnupiravir, it sometimes interprets it as C and sometimes as U. This causes more mutations in all subsequent copies than the virus can survive, an effect called viral error catastrophe or lethal mutagenesis.