LECTURE 26: ANTIVIRAL AGENTS
Katzung, Chapter 49

Learning Objectives

1. Be familiar with the mechanisms of viral replication and where drugs may act to inhibit this process.
2. Recall the antivirals used to treat each of the discussed viral infections.
3. Recognize the drugs used for treatment of HSV and VZV, their mechanisms of action, mechanism of viral resistance and adverse side effects.
4. Recognize the drugs used for treatment of cytomegalovirus and/or herpes, their mechanisms of action, mechanism of viral resistance and adverse side effects.
5. Recognize the drugs used for treatment of influenza, their mechanisms of action, mechanism of viral resistance and adverse side effects.
6. Recognize the drug used for treatment of RSV, its mechanisms of action, mechanism of viral resistance and adverse side effects.
7. Recognize the drugs used for treatment of HBV and HVC, their mechanisms of action, mechanism of viral resistance and adverse side effects.
8. Recognize the drugs used for treatment of COVID 19, their mechanisms of action, mechanism of viral resistance and adverse side effects.

HERPES SIMPLEX & VARICELLA-ZOSTER
Acyclovir (Zovirax)
Valacyclovir (Valtrex)
Docosanol (Abreva)

CMV/HERPES
Ganciclovir (Cytovene)
Valganciclovir (Valcyte)
Foscarnet (Foscavir)

INFLUENZA
Oseltamivir (Tamiflu)
Zanamivir (Relenza)

RSV
Ribavirin (Virazole)
Palivizumab (Synagis)

HEPATITIS B
Tenofovir (Viread)
Entecavir (Baraclude)
Lamivudine (Epivir)

COVID-19
Remdesivir (Veklury)
Molnupiravir (Lagevrio)
Nirmatrelvir and ritonavir (Paxlovid)

HEPATITIS C
Sofosbuvir/Ledipasvir (Harvoni)
Sofosbuvir/Velpatasvir (Epclusa)

What is a virus?

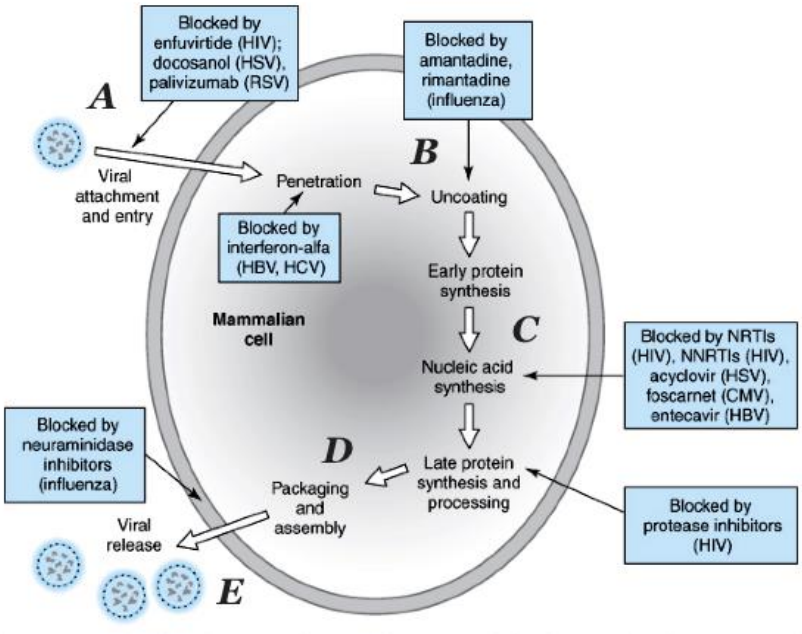
- A virus contains one or more strands of DNA or RNA, often with an outer protein or lipoprotein coat.
- They are intracellular parasites, and must enter a cell to reproduce and use the machinery of the cell. Because of this, it is very hard to develop drugs that will specifically kill viruses without harming the host
- Drugs act by preventing entry of viruses into cells, block replication of virus in the cell, where it may also kill the cell
- Drugs are targeted to characteristics that are specific to the virus, to decrease the likelihood of toxicity to the host.

Three approaches are used for treatment of prevention of viral diseases:

- immunological control (vaccination)
- stimulation of natural resistance mechanisms in the host
- chemotherapy

Viral Replication: Stages

1. ***attachment and penetration***: virus attaches to specific receptors on host cell and becomes internalized
2. ***uncoating***: protein coat of the virus is dissolved by viral enzymes to liberate viral RNA or DNA
3. ***synthesis of viral components***: virus takes over host cell nucleus and replicates its DNA or RNA, then makes proteins
4. ***packaging and assembly of virus particle***: viral genome may be encapsulated by viral protein, multiple membranes, or no protein
5. ***release of virus***: some viruses are released rapidly and kill the host cell; others are released slowly and allow the cell to survive.



Drugs used for treatment of HSV and VZV

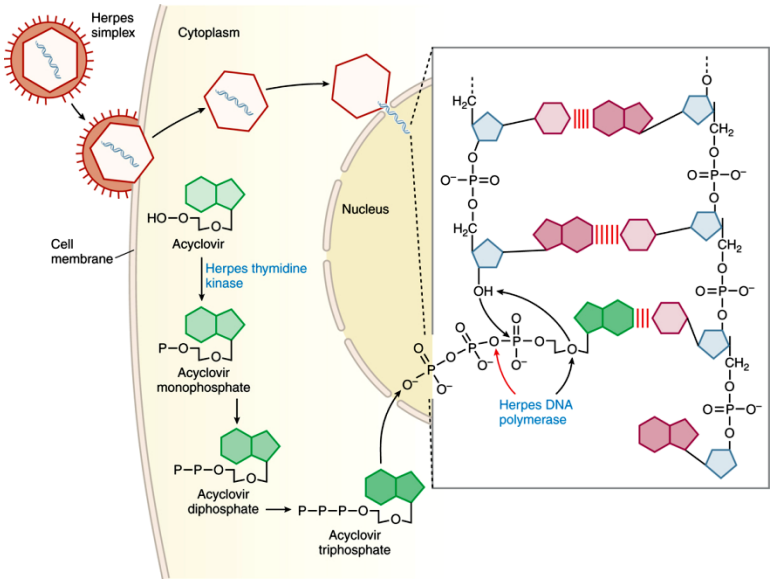
Acyclovir (Zovirax®)
Valacyclovir (Valtrex®)
Docosanol (Abreva®)

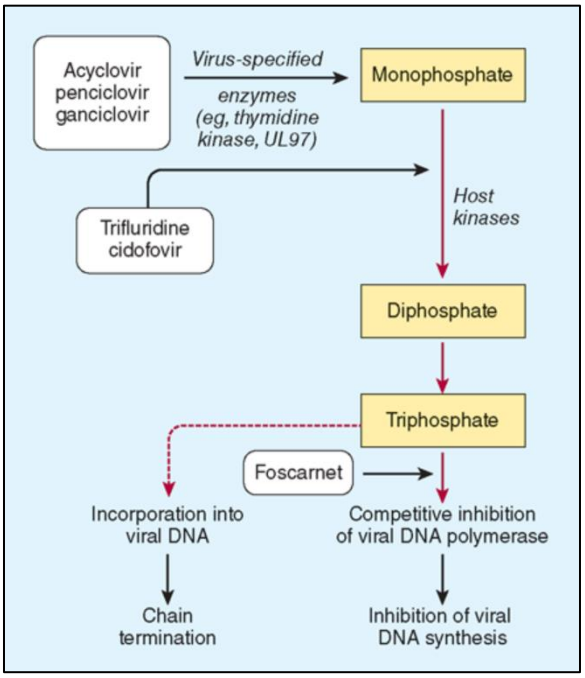
Herpes simplex virus (HSV) causes a variety of oral mucosal lesions. These include herpetic gingivostamatitis, recurrent intraoral herpes simplex, herpes labialis, herpes zoster and eczema herpeticum. The majority of herpes infections are treated with **acyclovir or oral valacyclovir.** Intravenous treatment may be needed if the herpes infection is severe or life-threatening.

ACYCLOVIR (Zovirax®), VALACYLOVIR (Valtrex)

Mechanism of action:

- Synthetic guanosine derivative
- **To be active, the drug must be phosphorylated three times**.
- The first phosphorylation event is done by **viral thymidine kinase** which allows uptake into cell
- The second and third phosphorylation step is done by **host** enzymes allows for competition with **deoxyGTP**
- **inhibits viral DNA polymerase;** causes chain termination, which **stops DNA replication**





Pharmacokinetics:

Acyclovir:

- oral, topical or IV
- decreased renal function may require alterations in drug dose

Valacyclovir

- **pro-drug** with high bioavailability which is given **orally** and **converted to acyclovir**
- bioavailability of valacyclovir compared to acyclovir was 3.3 to 5 times greater providing higher serum levels and thus higher effectiveness.

Therapeutic Use:

HSV (1 & 2)

- **herpetic gingivostamatitis and recurrent intraoral herpes simplex**.
- **eczema herpeticum** - long term suppressive treatment
- **herpes keratitis -** treatment (oral) and prophylaxis
- **genital herpes** – treatment of initial episodes, oral and topical; Long-term suppression of genital herpes - decreases symptomatic recurrences and asymptomatic viral shedding (decreasing transmission).
- IV administration used for herpes simplex encephalitis or neonatal herpes and chronic or recurrent mucocutaneous HSV infections in immuno-compromised patients.
- used prophylactically in patients undergoing **organ transplant** or in immuno-compromised

VZV – chicken pox and shingles

Side Effects

- low toxicity - because acyclovir is **concentrated in virally infected cells**, it is virtually **non-toxic** to normal cells at therapeutic doses
- nausea, diarrhea, headache (rarely)
- high IV dose may cause **renal** tubular obstruction; this is avoided by **hydration** and slow infusion.
- **safe for use in pregnancy**

Resistance:

- resistance can develop; viruses may **decrease their level of thymidine kinase or alter the DNA polymerase**
- IF resistance is due to deficiencies in viral thymidine kinase, **cross resistance will occur with valacyclovir** and ganciclovir. Use agents such as foscarnet and cidofovir which do NOT require viral thymidine kinase.

DOCOSANOL (Abreva®)

- **Inhibits fusion** between host cell plasma membrane and the herpes simplex virus (HSV) envelope
- **Prevents entry** of virus into the cell
- Topical - for treatment of **cold sores**
- Available over the counter (OTC)
- May irritate skin or cause headache

Drugs used to treat Cytomegalovirus (CMV) and/or Herpes

Ganciclovir (Cytovene®); Valganciclovir (Valcyte)
Foscarnet (Foscavir®)

GANCICLOVIR (Cytovene®); VALGANCICLOVIR (Valcyte®)

Mechanism of action:

- synthetic analogues of guanosine, very similar to acyclovir, but slightly more toxic
- **phosphorylated by thymidine kinase in cells infected with herpes, and by viral protein kinase phosphotransferase in CMV infected cells**
- once phosphorylated, inhibits DNA polymerase, **suppresses DNA chain elongation** and inhibits CMV replication

Pharmacokinetics:

- Ganciclovir - IV or intraocular implant/gel
- Valganciclovir – oral; pro-drug with much higher absorption than ganciclovir

Uses:

- **Oral -** for prophylaxis and therapy of **CMV** infections
- **IV** - life- or sight-threatening **CMV** infections
- **Ocular implant or intravitral injection** which lasts 5-8 months is available for treatment of **CMV retinitis**
- **Gel – herpes simplex keratitis**
- transplant patients to reduce risk of developing CMV

Toxicity:

- **myelosuppression**, mainly when high doses given **IV,** especially when **combined with zidovudine**
- other adverse effects include fever, rash, phlebitis, diarrhea, confusion, headache, coma, seizures, and abnormal liver function tests
- **CNS effects** – abnormal dreams, anxiety, confusion, tremor, seizures (rare)

FOSCARNET (Foscavir®)

- **directly** inhibits **HSV DNA and RNA polymerase** and **HIV reverse transcriptase –** does NOT required phosphorylation to become activated.
- **used to treat acyclovir-resistant herpes** infections and **CMV retinitis or encephalitis** (often in AIDS patients)
- **IV** only; may be combined with ganciclovir for synergistic effect
- **Nephrotoxic (33% of patients)** - doses of foscarnet should be based on creatinine clearance, incidence of toxicity is decreased by hydration
- malaise, nausea, vomiting, fatigue, headache, CNS disturbances, seizures, hallucinations
- genital ulcers may occur from high levels in urine, especially in men

CIDOFOVIR (Vistide®) – FYI only

Mechanism of action:

- cytosine analogue
- phosphorylation to an active drug is **independent of viral enzymes; activity is maintained against kinase-deficient CMV or HSV**

Pharmacokinetics:

- **IV** – CMV retinitis
- **IV** or topical – acyclovir-resistant HSV

Adverse effects:

- **Dose-dependent nephrotoxicity** - aggressive prehydration and adjunctive hydration required
- Avoid use with other nephrotoxic drugs (aminoglycosides, amphotericin B, pentamidine)

Drugs used to treat Influenza

Oseltamivir (Tamiflu®)/Zanamivir (Relenza®)
Baloxavir marboxil (Xofluza)

OSELTAMIVIR (Tamiflu®) and ZANAMIVIR (Relenza®)

Mechanism of action:

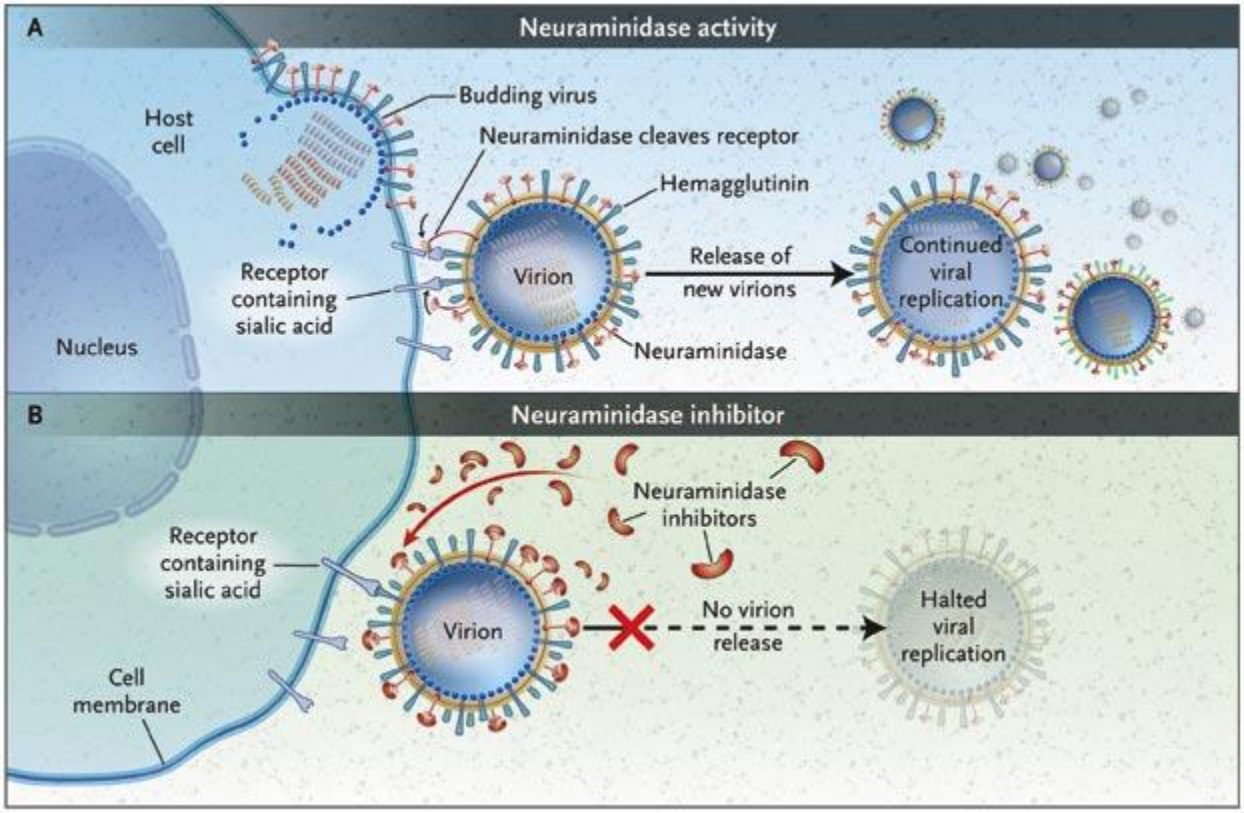
- **neuraminidase inhibitors** selective for influenza A and B
- neuraminidase cleaves a sialic acid residue, which is essential for release of the virus from infected cells, and subsequent spread to other cells
- these drugs **inhibit release of virus from infected cells**

Therapeutic use:

- Oseltamivir is given **orally**; prodrug that is activated in the gut and liver, and excreted by the kidney; also used for treatment of bird flu. Treatment is initiated 36-48 h after onset of symptoms, and lasts for 5 days.
  - Approved for patients >1 yr
- Zanamivir is given **oral inhaler** for direct delivery to the respiratory tract (not well absorbed orally). Treatment is initiated 36-48 hr after onset of symptoms, and lasts for 5 days
  - Approved for patients > 7 years

Side effects

- Oseltamivir may cause **nausea and vomiting**, which is reduced if it is taken with food.
- Zanamivir may **worsen respiratory function** in patients with chronic obstructive pulmonary disease or cause **bronchospasm** in asthmatics, and causes nasal and throat discomfort.



BALOXAVIR MARBOXIL (Xofluza) – FYI only

Xofluza is the newest anti-influenza drug, approve in October 2018

Mechanism: inhibits the endonuclease activity of polymerase acidic (PA) protein, an influenza virus-specific enzyme in the viral RNA polymerase complex. By blocking the PA protein, baloxavir **prevents viral gene transcription and ultimately influenza virus replication**

Clinical use:

- Oral
- Active against influenza A and B, approved for the treatment of acute uncomplicated influenza
- Start within 48 h of symptom onset
- approved for patients >12 years old
- Single dose

Adverse effects:

- Diarrhea, nausea, headache
- Approve October, 2018
- More will come as the drug is prescribed more.

Treatment of Coronavirus; COVID-19

Remdesivir (Veklury)
Molnupiravir (Lagevrio)
Nirmatrelvir and ritonavir (Paxlovid)

REMDESIVIR (Veklury)

Mechanism of action:

- adenosine analog (RDV-TP) that inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses causing chain termination and inhibition of viral replication

Pharmacokinetics

- IV

Therapeutic uses:

- **approved** for the treatment of adults and pediatric patients ≥28 days and weighing ≥3 kg requiring hospitalization for COVID-19

Toxicity

- nausea, hepatic enzyme changes…new drug, so many unknowns

MOLNUPIRAVIR (Lagevrio)

Mechanism of action:

- ribonucleoside analog that causes RNA mutations and inhibits the replication of SARS-CoV-2

Pharmacokinetics

- oral (5 days of treatment)

Therapeutic uses:

- Broad spectrum activity against RNA viruses
- Emergency use authorized for adults > 18yrs; reduces risk of hospitalization or death by 50%

Toxicity

- nausea, GI, dizziness…another new drug, so many unknowns

PAXLOVID

Mechanism of action:

- Combination of nirmatrelvir and ritonavir
- Nirmatrelvir – protease inhibitor
- Ritonavir –inhibits CYP3A4 to boost plasma concentrations of Nirmatrelvir (pharmacoenhancer)

Pharmacokinetics

- oral (5 days of treatment)

Therapeutic uses:

- Emergency use authorized for adults; reduces risk of hospitalization or death by 50%

Toxicity

- Viral rebound
- Altered taste, diarrhea, nausea, muscle aches…
- Drug interactions (ritonavir)

Treatment of Respiratory Syncytial Virus (RSV)

Ribavirin (Virazole®)
Palivizumab (Synagis)

RIBAVIRIN (Virazole®)

Mechanism of action:

- purine nucleoside analogue, structurally similar to guanosine; **inhibits viral mRNA synthesis**, protein synthesis and viral replication

Pharmacokinetics

- aerosol, IV, oral

Therapeutic uses:

- **aerosol** to hospitalized infants and young children with severe **RSV** lower respiratory tract infection
- **oral** with **interferon-alfa 2b or 2a** for treatment of **hepatitis C**, where it doubles the likelihood of response to interferon
- **IV** - lassa fever, West Nile.

Toxicity

- **Pregnancy category X – teratogenic:** both patient and partner must avoid pregnancy
- **Psychiatic** - **depression and suicide** are more frequently associated with systemic use, particularly among pediatric patients/adolescents. Also occurs oral use, but with less frequency.
- aerosol - **cardiac arrest,** dyspnea, chest soreness, hypotension
- oral - **dose-dependent hemolytic anemia (reduce dose),** headache, GI problems, insomnia, lethargy, dyspnea,

Caution! Ribavarin may be absorbed passively by staff working with patients during aerosol treatment. Pregnant women must not administer it! Data on sperm containment resulting in teratogenesis is unknown.

PALIVIZUMAB (Synagis)

Mechanism of action

- monoclonal antibody that binds to the RSV envelope fusion protein (RSV F) to neutralizing and inhibit host cell fusion

Therapeutic use:

- RSV prophylaxis; confers passive immunity to high risk patients
- Injected once a month
- Well tolerated; fever and rash are the most common effects.

Treatment of Hepatitis B

- Acute **hepatitis B** is generally self-limiting. There are now several oral drugs available for treatment of chronic HBV. **All of them are reverse transcriptase inhibitors that also inhibit HBV DNA polymerase**; doses are much lower that for the treatment of HIV.
- Interferon-alfa2b was the first drug used to treat chronic HBV, but it has been replaced by oral drugs which are much better tolerated.
- Patients generally receive treatment if HBV RNA is greater than 2000 copies/ml, and treatment will be continued for life. The goal of treatment is seroconversion of HBsAg from positive to negative, and the levels of HBV below 5 log copies/ml.

Many of the oral drugs are also used for treatment of HIV, and are helpful in patients with co-infections

TENOFOVIR (Viread)

- currently the drug of choice for HBV
- well tolerated; nausea, dizziness, fatigue, depression
- high response rate and low rate of resistance

ENTECAVIR (Baraclude)

- high rate of suppression, low resistance, well tolerated.
- hepatic encephalopathy and elevated liver enzymes can occur, but is rare.

LAMIVUDINE (Epivir)

- resistance is common after 5 years of treatment.
- Headache, nausea, fatigue, pancreatitis (rare)

Treatment of Hepatitis C

- Hepatitis C became an epidemic in the US, affecting about 3-4 million people. Current recommendations are that all people born between 1945-65 should be tested, as well as anyone with known risk factors.
- The earliest treatment of HCV was interferon-alfa2b, combined with ribavirin. Side effects were significant and the success rate was low (especially for genotype 1, the most common genotype in the US).
- Several new drugs were approved in the last few years which as greatly changed the management of this disease, as is expected to greatly reduce the necessity for liver transplants due to complications of this disease.
- treatment regimens are based on genetype (1-6).

Both Epclusa and Harvoni have cure rates >95%

SOFOSBUVIR/LEDIPASVIR (Harvoni)
SOFOSBUVIR/VELPATASVIR (Epclusa)

Sofosbuvir – nucleoside analogue (uridine); inhibits viral NS5B RNA polymerase, blocking replication of HCV when the uridine analogue is incorporated, causing termination. NO effect on human or mitochondrial RNA polymerase, thus side effects are low.

Ledipasvir and Velpatasvir – inhibits HCV NS5A protein, may block viral hyperphosphorylation. Exact mechanism is still unknown.

Sofosbuvir/Ledipasvir (Harvoni)

- This combination was approved by the FDA in October 2014 – genotype 1
- Once daily tablet, 12 week treatment is ~$95,000

Sofosbuvir/Velpatasvir (Epclusa)

- This combination was approved by the FDA in June 2016 – genotype 1

Toxicities associated with Harvoni and Epclusa

- fatigue, headache, irritability
- May be combined with ribavirin
- New drugs…more toxicities are sure to arise in the future!

SUMMARY

Virus	Drug of first choice	Alternate
HSV	Acyclovir/valacyclovir	Ganiclovir/valganciclovir Docosanol (OTC) Foscarnet Cidofovir
VZV	Acyclovir/valacyclovir	
CMV	Ganiclovir/valganciclovir Foscarnet + ganciclovir (encephalitis)	Foscarnet (retinitis) Cidofovir (retinitis)
Influenza	Zanamivir (inhaler) or Oseltamivir (oral)	Baloxavir marboxil (Xofluza)
RSV	Ribavirin	
Hepatitis B	Entecavir Tenofovir	Lamivudine
Hepatitis C	Sofosbuvir/Ledipasvir (Harvoni) Sofosbuvir/Velpatasvir (Epclusa)	
Coronavirus; COVID-19	Remdesivir (Veklury) Molnupiravir Paxlovid	