PYCH305 Pharmacology II

# Antiviral & Anti-HIV drugs

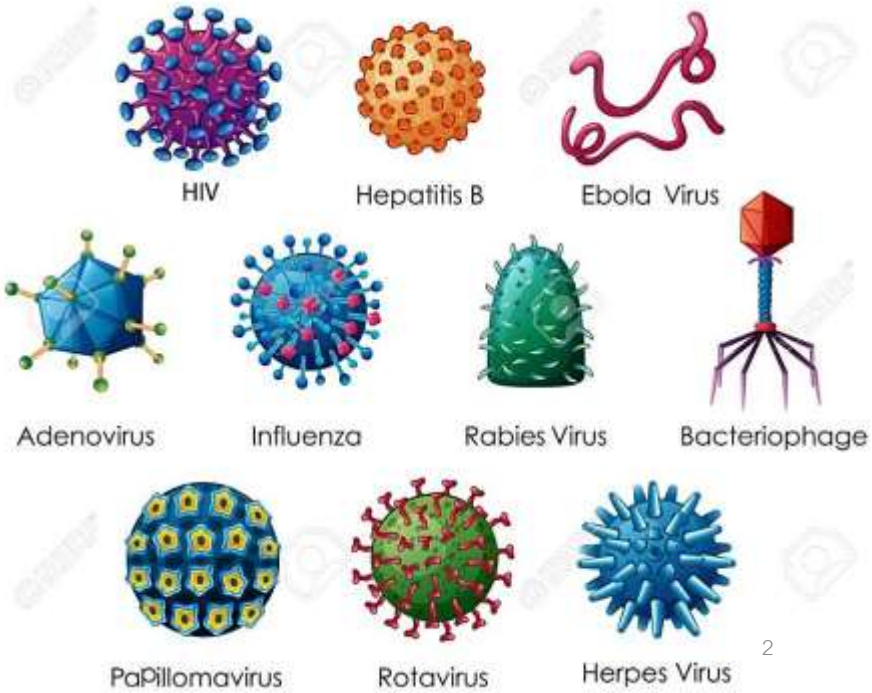
**Warisara Parichatikanond, PhD, Dr.Scient.Med.**

**Department of Pharmacology**

**Faculty of Pharmacy, Mahidol University**

# INTRODUCTION: Antiviral drugs

- Viral infections are the leading causes of morbidity & mortality worldwide. Public health measures & prophylactic vaccines remain in demand to control the spread of viral infections
- Acquired immunodeficiency syndrome (AIDS) continues to be a common cause of death (African: 1/5 infected)
- Because viruses are obligate intracellular parasites, identification of safe & effective antiviral therapies is difficult
- The best antiviral drugs inhibit a specific step in viral replication
- Combination of targeted delivery to control toxicities & resistance



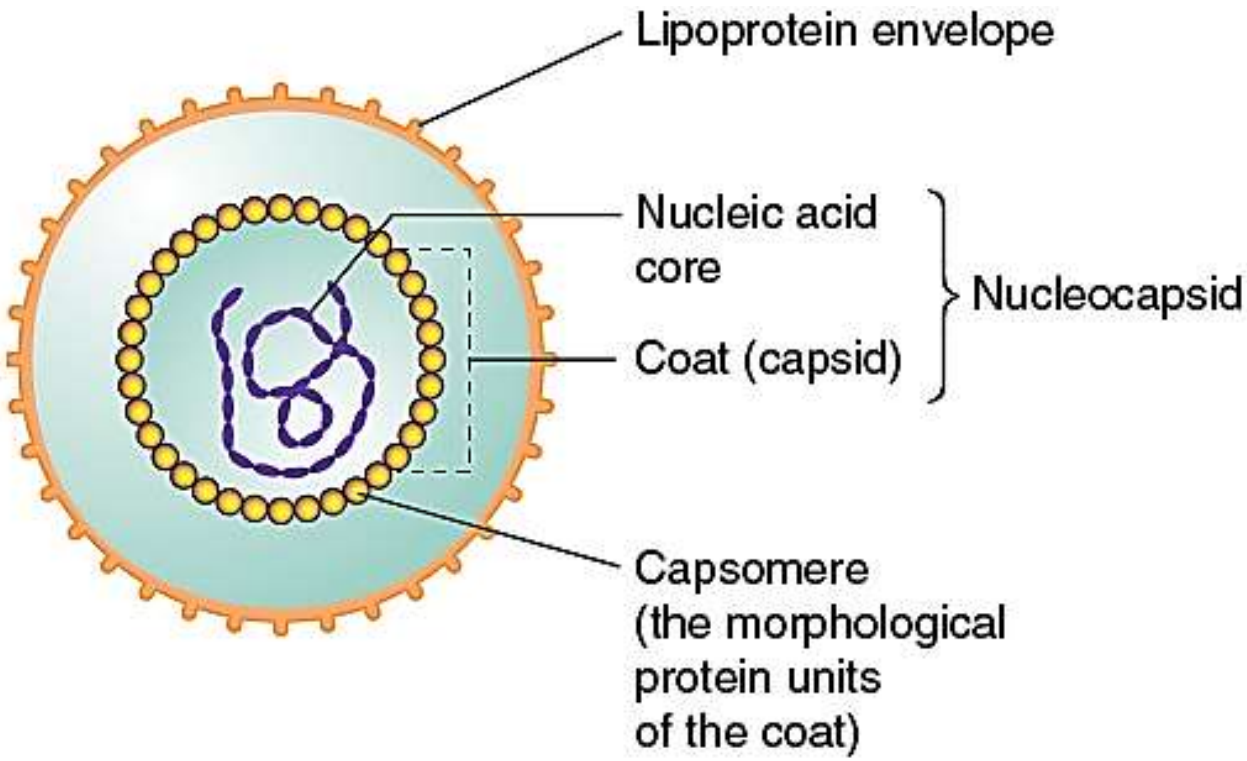
# Antiviral therapy challenging

- *Rapid replication* of viruses makes it difficult to develop effective antiviral
- Viruses can rapidly *mutate* and drug becomes ineffective (*resistance*)
- Difficulty for drug to target virus *without injuring normal cells* -> may interfere host cells function and result in toxicity

- Most current antiviral drugs exploit differences between structures and functions of viral proteins and human proteins to achieve "selectivity of antiviral action"
- Antiviral drugs are "virustatic": Inhibit viral replication/entry temporarily (reversible) and do not affect latent virus

# Viruses

- **Viruses are small infective agents (20-30 nm) consisting of nucleic acid (RNA or DNA) enclosed in a protein coat**
- **They are not cells and, having NO metabolic machinery of their own, are obligate intracellular parasites, utilizing the metabolic processes of host cell they infect to replicate**




Rang & Dale's Pharmacology. 9th. 2021.

Overview of

# Viral infections

**Encephalitis/ meningitis**
- JC virus
- Measles
- LCM virus
- Arbovirus
- Rabies

**Common cold**
- Rhinoviruses
- Parainfluenza virus
- Respiratory syncytial virus

**Eye infections**
- Herpes simplex virus
- Adenovirus
- Cytomegalovirus

**Parotitis**
- Mumps virus

**Pneumonia**
- Influenza virus, Types A and B
- Parainfluenza virus
- Respiratory syncytial virus
- Adenovirus
- SARS coronavirus

**Pharyngitis**
- Adenovirus
- Epstein-Barr virus
- Cytomegalovirus

**Gingivostomatitis**
- Herpes simplex type 1

**Cardiovascular**
- Coxsackie B virus

**Hepatitis**
- Hepatitis virus types A, B, C, D, E

**Myelitis**
- Poliovirus
- HTLV-I

**Skin infections**
- Varicella zoster virus
- Human herpesvirus 6
- Smallpox
- Molluscum contagiosum
- Human papillomavirus
- Parvovirus B19
- Rubella
- Measles
- Coxsackie A virus

**Gastroenteritis**
- Adenovirus
- Rotavirus
- Norovirus
- Astrovirus
- Coronavirus

**Sexually transmitted diseases**
- Herpes simplex type 2
- Human papillomavirus
- HIV

**Pancreatitis**
- Coxsackie B virus

# Viruses

## *DNA viruses*

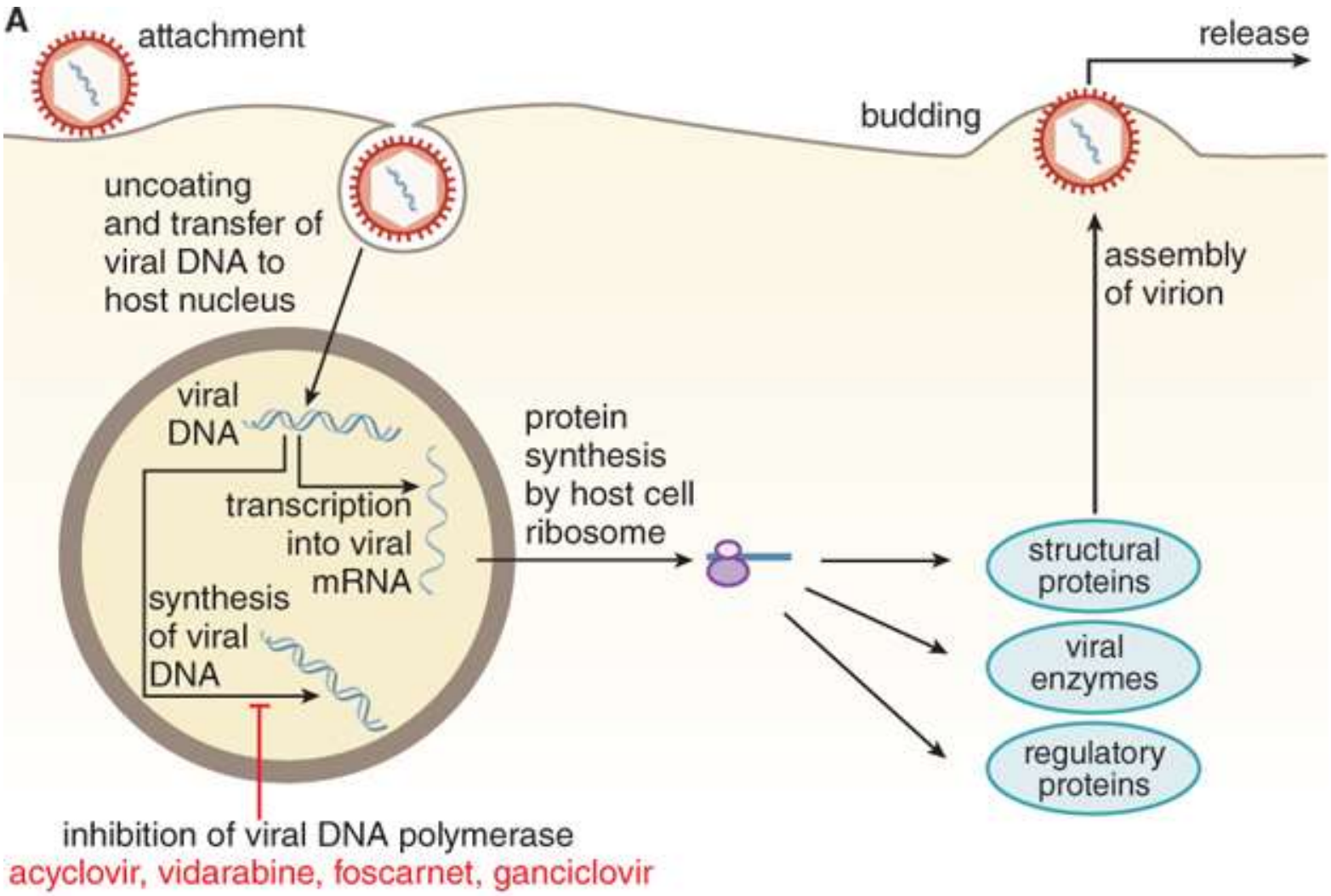
- Enter host cell nucleus and direct generation of new viruses
- Example: poxviruses (smallpox), herpesviruses (chickenpox, shingles, oral/genital herpes), adenoviruses (conjunctivitis, sore throat), hepadnaviruses (hepatitis B), papillomaviruses (warts)

## *RNA viruses*

- Direct generation of new viruses usually without incorporated into host cell genome (Others- Cytosol, Influenza virus- Host cell nucleus)
- Example: rubella virus (German measles), rhabdoviruses (rabies) picornaviruses (poliomyelitis, meningitis, hepatitis A), flaviviruses (yellow fever, hepatitis C), orthomyxoviruses (influenza), paramyxoviruses (measles, mumps), coronaviruses (colds, SARS)
- *RNA retroviruses* (e.g. AIDS, T-cell leukaemia) contain an enzyme, reverse transcriptase (makes a DNA copy of viral RNA) -> DNA copy is integrated into host cell genome -> directs generation of new virus particles

# Replicative cycles of DNA viruses

## *Herpesvirus*



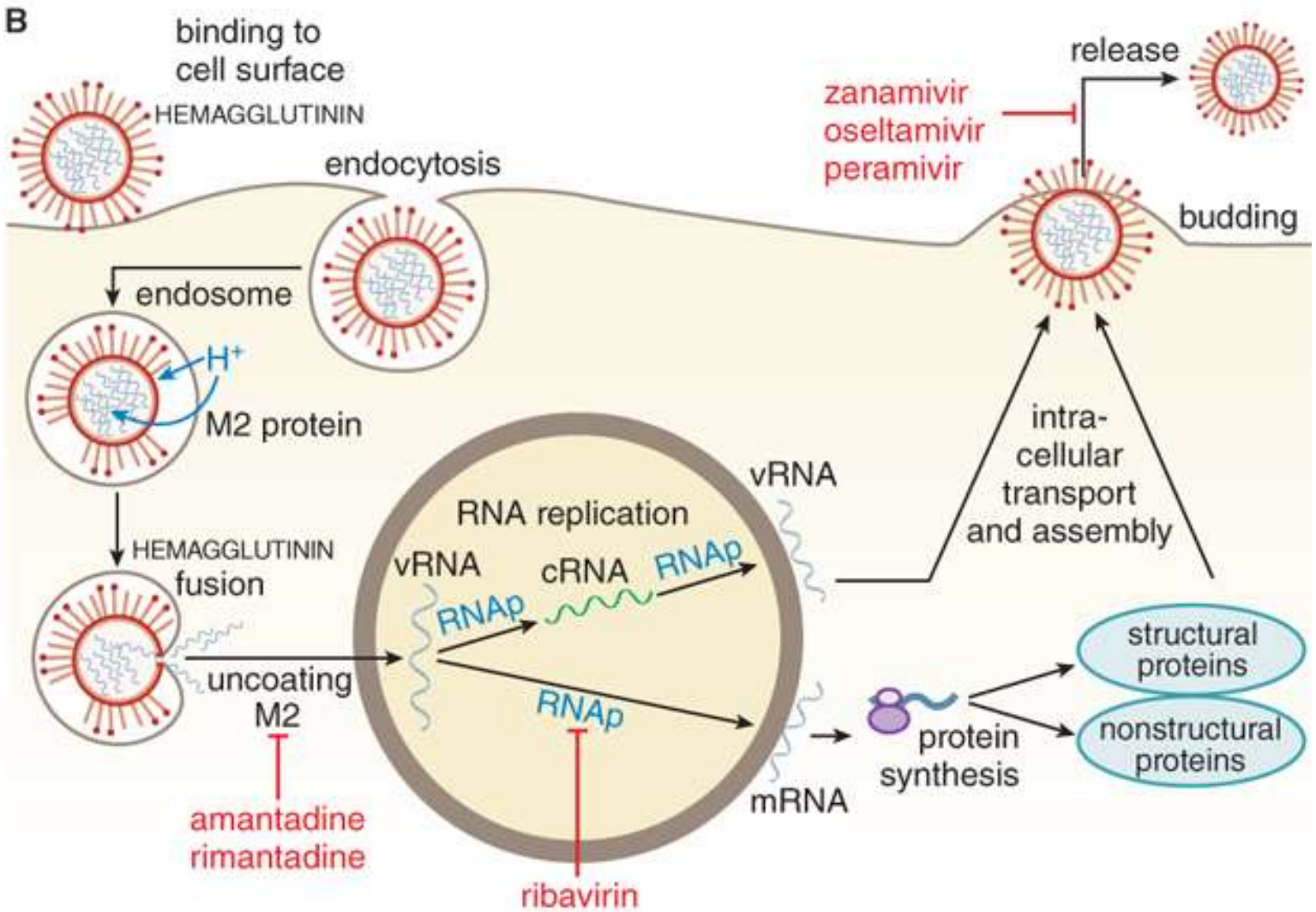



Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Replicative cycles of RNA viruses

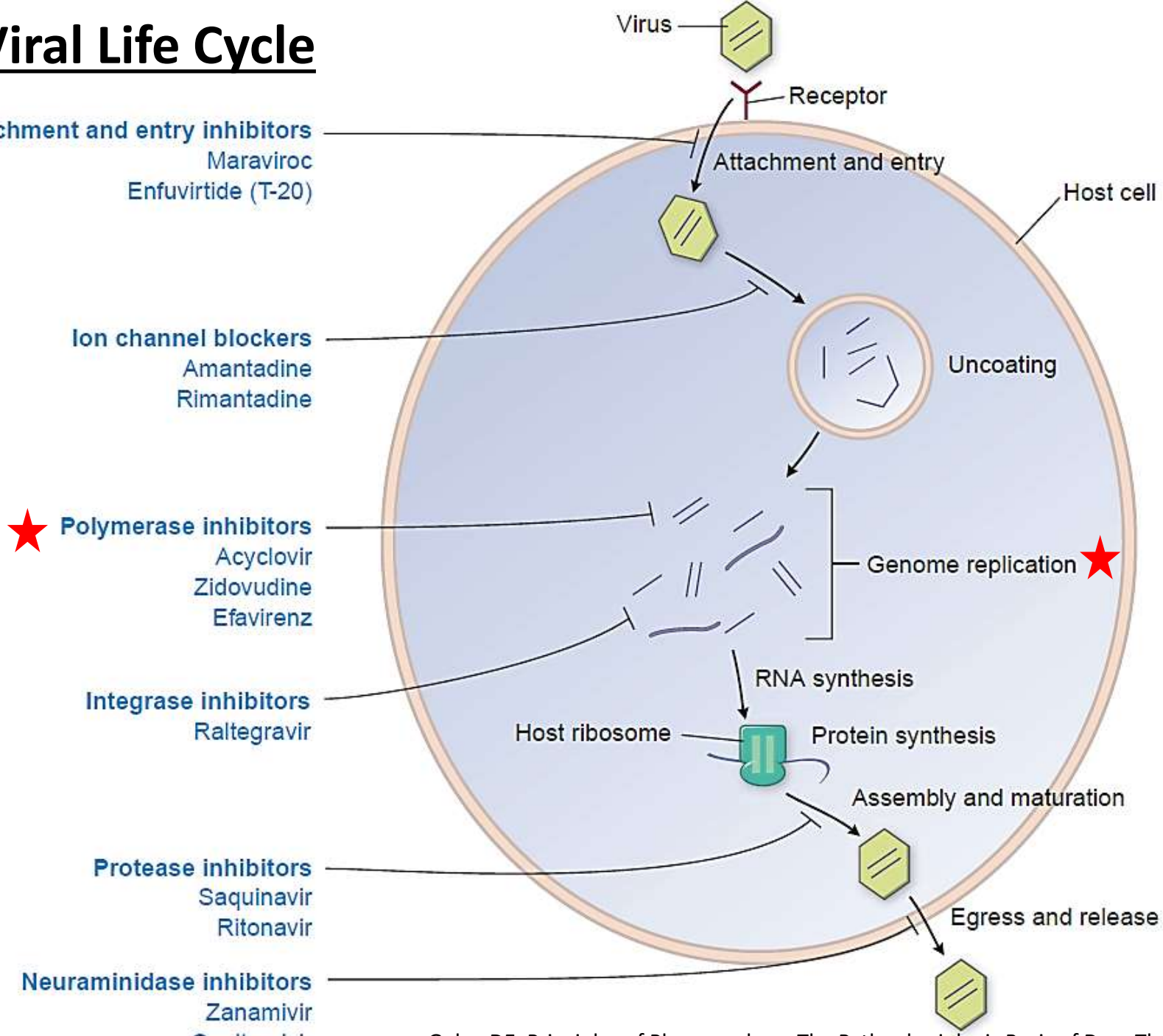
Airway epithelial cell

## *Influenza*




Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Viral Life Cycle





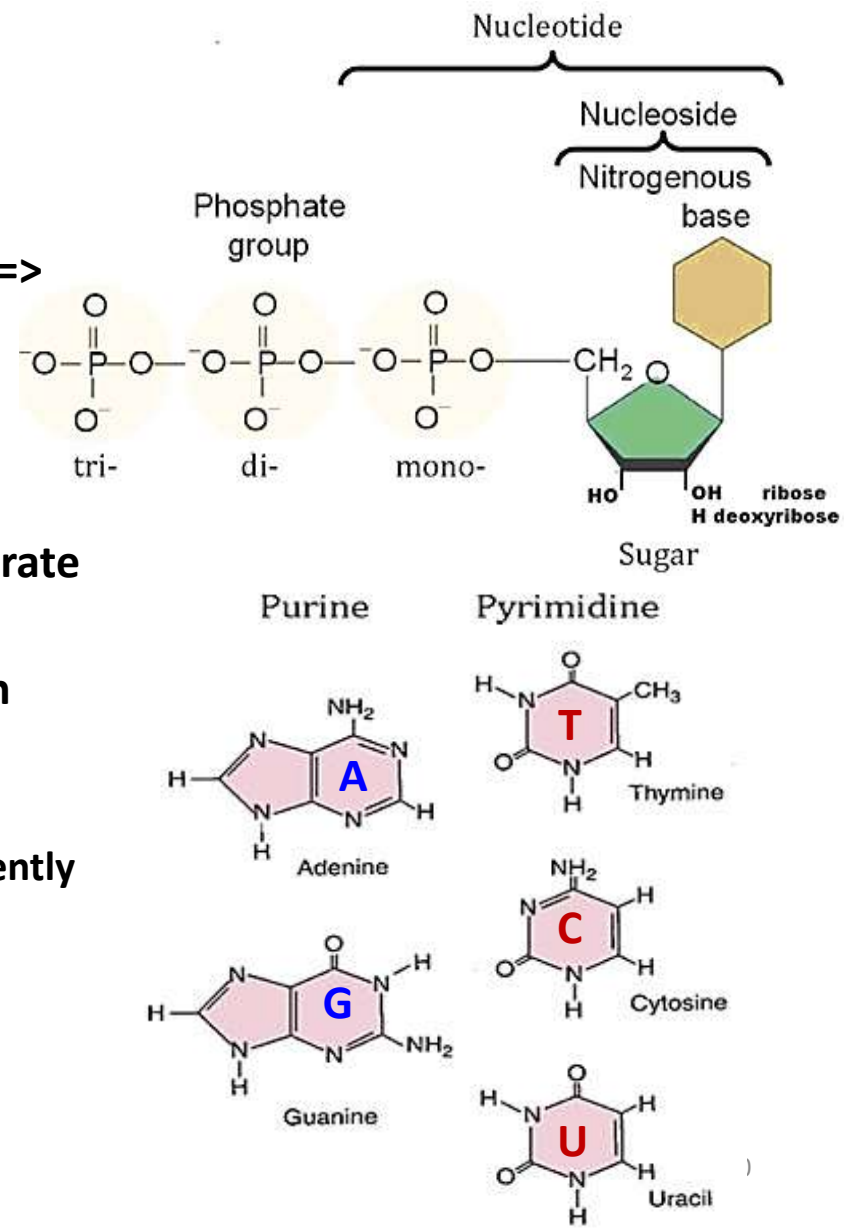

Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th, 2016

# Nucleoside analogues

- **Majority of drugs that inhibit viral genome replication inhibit "polymerase"**
- **All nucleoside analogues must be activated by phosphorylation, usually to triphosphate form => mimic deoxyribonucleoside triphosphates**

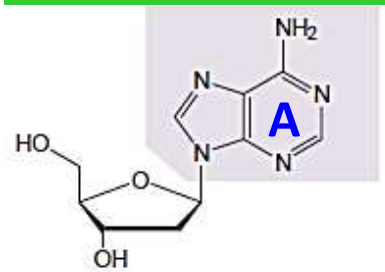
- **Antiviral activity of nucleoside analogues:**
  - **Enzyme inhibition: inhibit polymerase by competing with natural triphosphate substrate**
  - **Incorporation into DNA: incorporate into growing DNA chain -> terminate elongation**

- **Selectivity depends on**
  - **Kinase** (Activation step): **How much more efficiently viral enzymes *phosphorylate* drugs than cellular enzymes**
  - **Polymerase** (Inhibition step): **How much more potently and effectively viral DNA synthesis *is inhibited* than cellular functions**



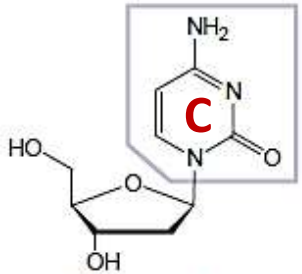
# Antiviral nucleoside and nucleotide analogues

## Native nucleoside analogues

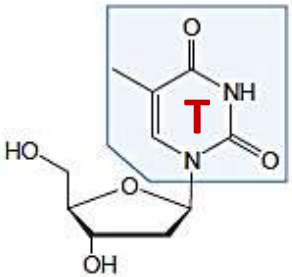



Deoxyadenosine

Deoxyguanosine

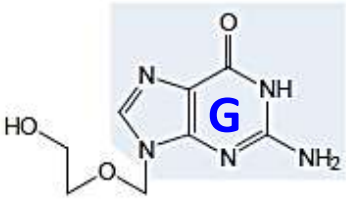



Deoxycytidine

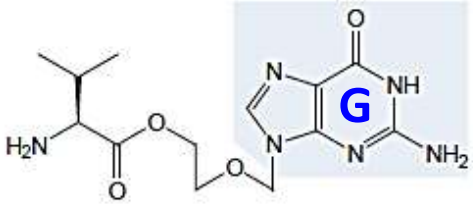



Deoxythymidine

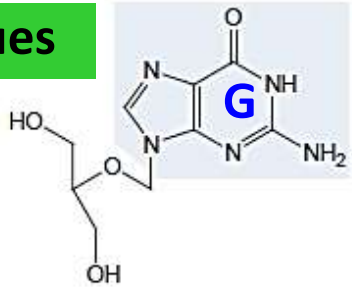
## Antiherpesvirus & CMV nucleoside analogues



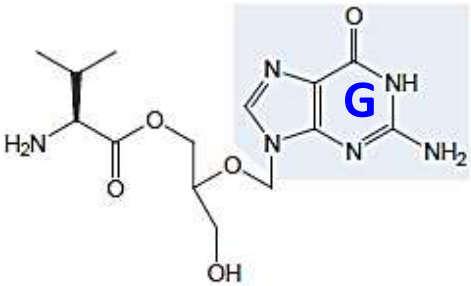

Acyclovir



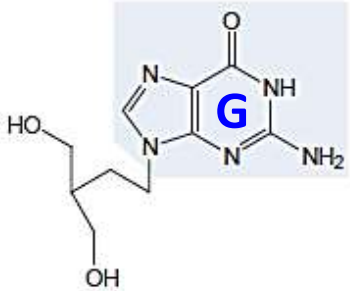

Valacyclovir
(prodrug)



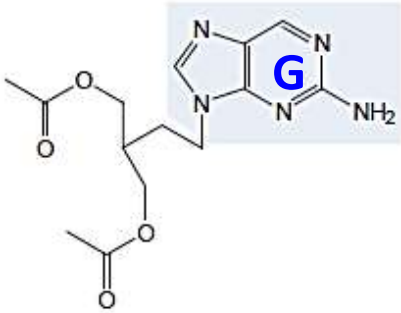

Ganciclovir



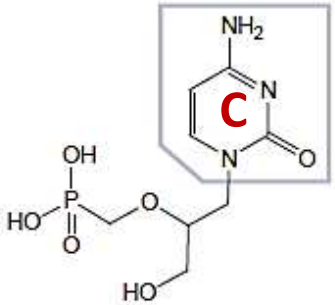

Valganciclovir
(prodrug)




Penciclovir




Famciclovir
(prodrug)

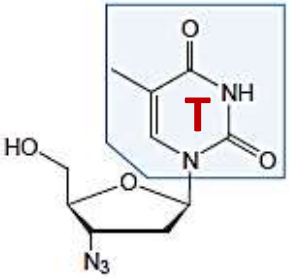



Cidofovir

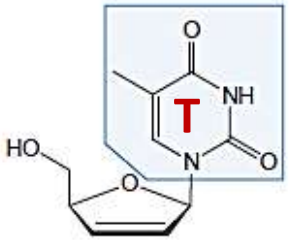
Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th, 2016

# Antiviral nucleoside and nucleotide analogues

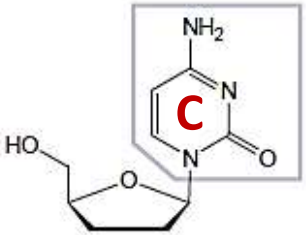
## Anti-HIV nucleoside analogues



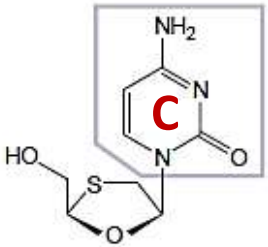

Zidovudine (AZT)



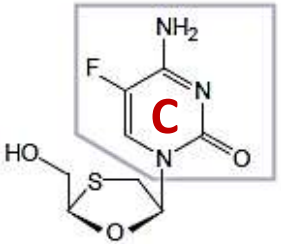

Stavudine (d4T)



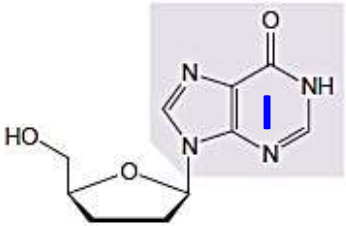

Zalcitabine (ddC)




Lamivudine (3TC)

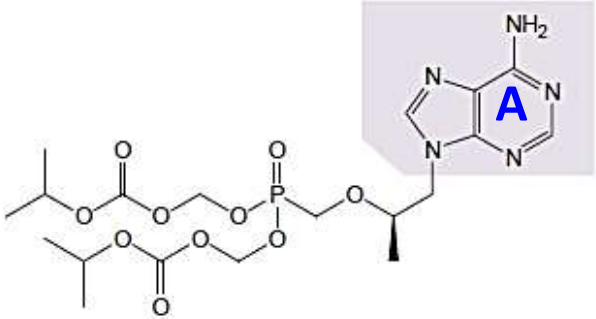



Emtricitabine (FTC)



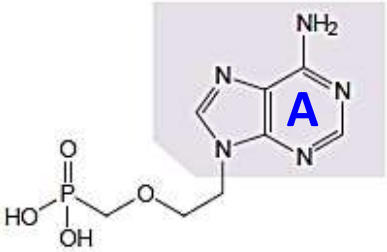

Didanosine (ddI)

Abacavir

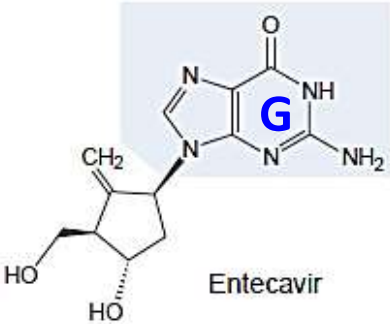



Tenofovir disoproxil

## Anti-hepatitis B nucleoside analogues

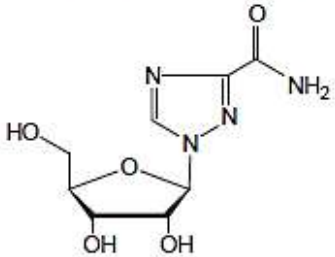



Adefovir




Entecavir

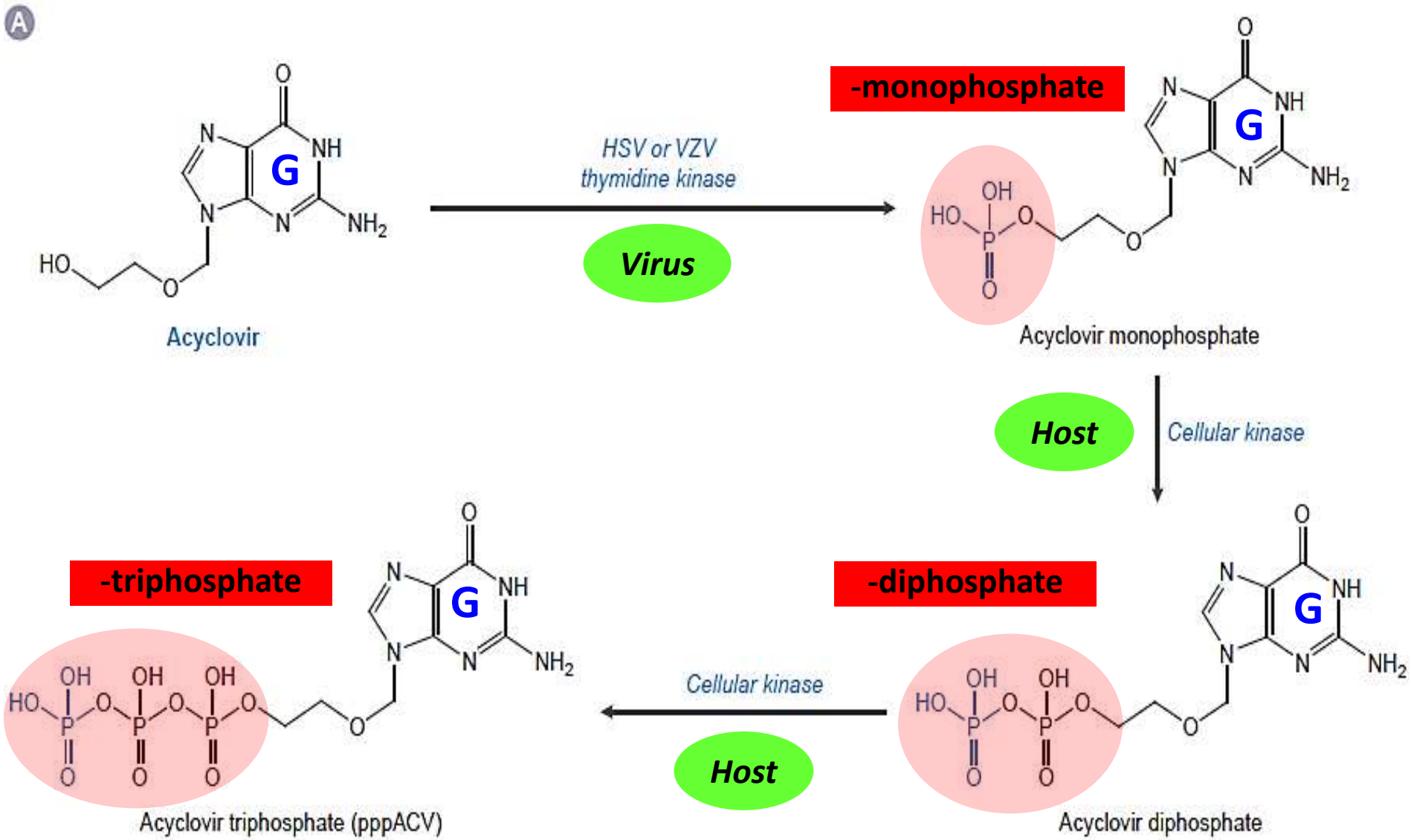
## Anti-RNA virus nucleoside analogues



Ribavirin

Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th, 2016

# Example of nucleoside analogue (Acyclovir)






Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th, 2016

# Selectivity of action of antiviral nucleoside analogues

**TABLE 37-1 Selectivity of Action of Antiviral Nucleoside Analogues Is Determined by Specificity of Viral and Cellular Kinases and Polymerases**

| DRUG | KINASE SPECIFICITY | POLYMERASE SPECIFICITY |
|---|---|---|
| Acyclovir | Viral TK >> Cellular kinases | Viral DNA polymerase >> Cellular DNA polymerase |
| Ganciclovir | Viral UL97 > Cellular kinases | Viral DNA polymerase > Cellular DNA polymerase |
| Zidovudine (AZT) | Cellular TK | Viral RT >> Cellular DNA polymerase |

Drugs are presented in order of selectivity of action: >>, large difference in specificity; >, modest difference in specificity. TK, thymidine kinase; RT, reverse transcriptase.

**Acyclovir is the most selective because it's highly selective at both activation (kinase) and inhibition (polymerase) step. AZT is the least selective because it's non-selective at activation.**



Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th, 2016

# Antiviral Drugs for Herpesvirus Infection

# Herpesvirus infection

## Herpes simplex virus (HSV)

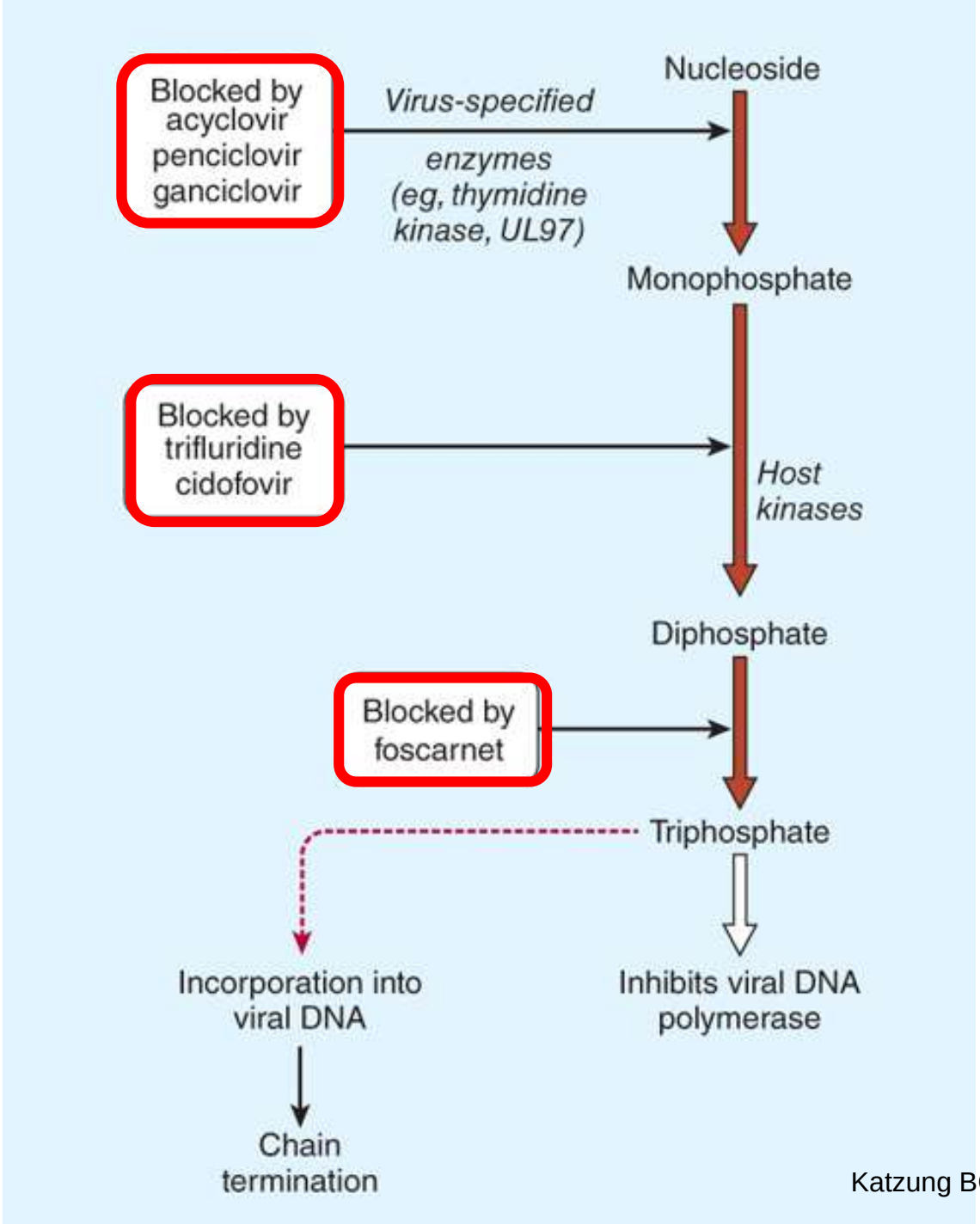
- **Disease:** Herpes genitalis (sexually transmitted diseases, STDs), Herpes orolabialis
- **Cause:** Herpes simplex virus (HSV), incubation period 7-14 days
  - HSV-1: Mouth, face, skin, esophagus, brain
  - HSV-2: Genitals, rectum, skin, hands, meninges
- **Sign & symptom:** mild
  - Multiple painful pustular or ulcerative lesions (7–10 days; heal in 2–4 weeks)
  - Others: Flu-like symptoms, local itching, pain, vaginal or urethral discharge, paresthesias, urinary retention

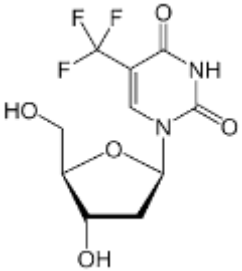
# Herpesvirus infection

## Varicella-zoster virus (VZV)

- **Disease:** Chickenpox (varicella), herpes zoster (shingles)
- **Cause:** Varicella-zoster virus (VZV) (contagious)
- **Sign & symptom:**
  - **Chickenpox:** Fever, headache, stomachache, loss of appetite (before breaking out in classic pox rash)
  - **Herpes zoster:** Painful rash (red, pain, burning) -> develops on one side of face or body -> blisters (scab over in 7-10 days)

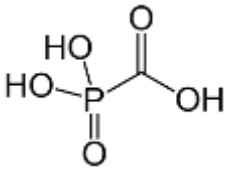
# Mechanism of action of antiherpes agents




**Trifluridine**

is phosphorylated within cells to trifluridine triphosphate (active)

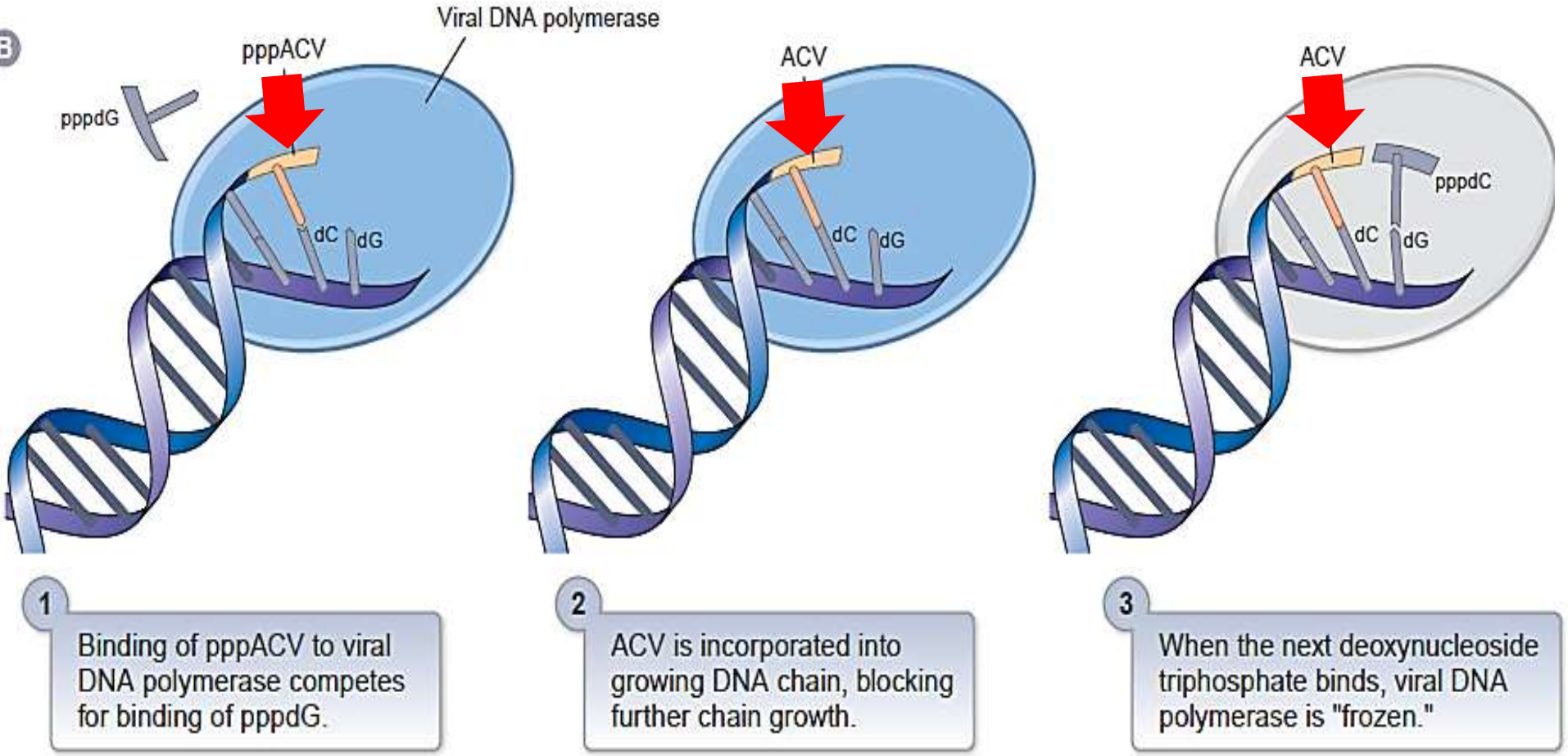



**Foscarnet**

mimic pyrophosphate -> selectively inhibits pyrophosphate binding site on viral DNA polymerases

Katzung BG: Basic and Clinical Pharmacology. 15th. 2021.

# Acyclovir triphosphate has 3 steps mechanism of inhibition of herpesvirus DNA polymerase

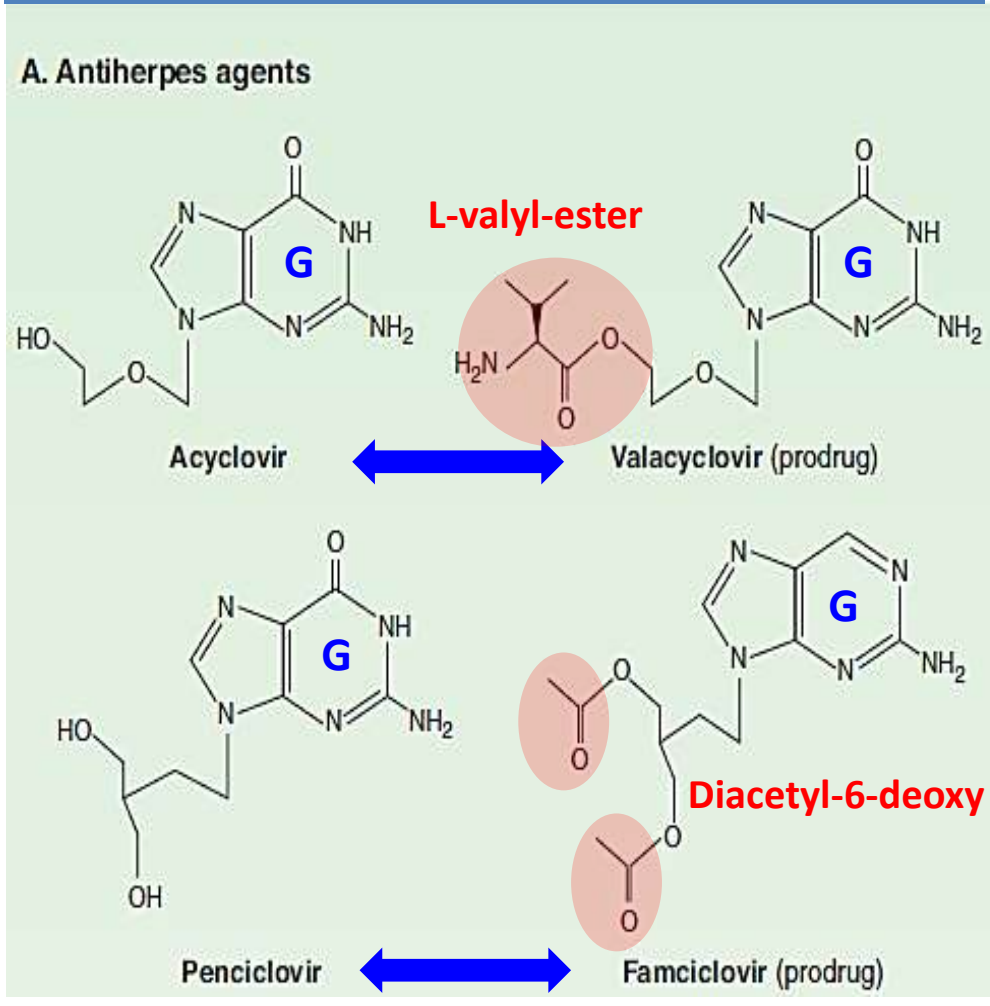




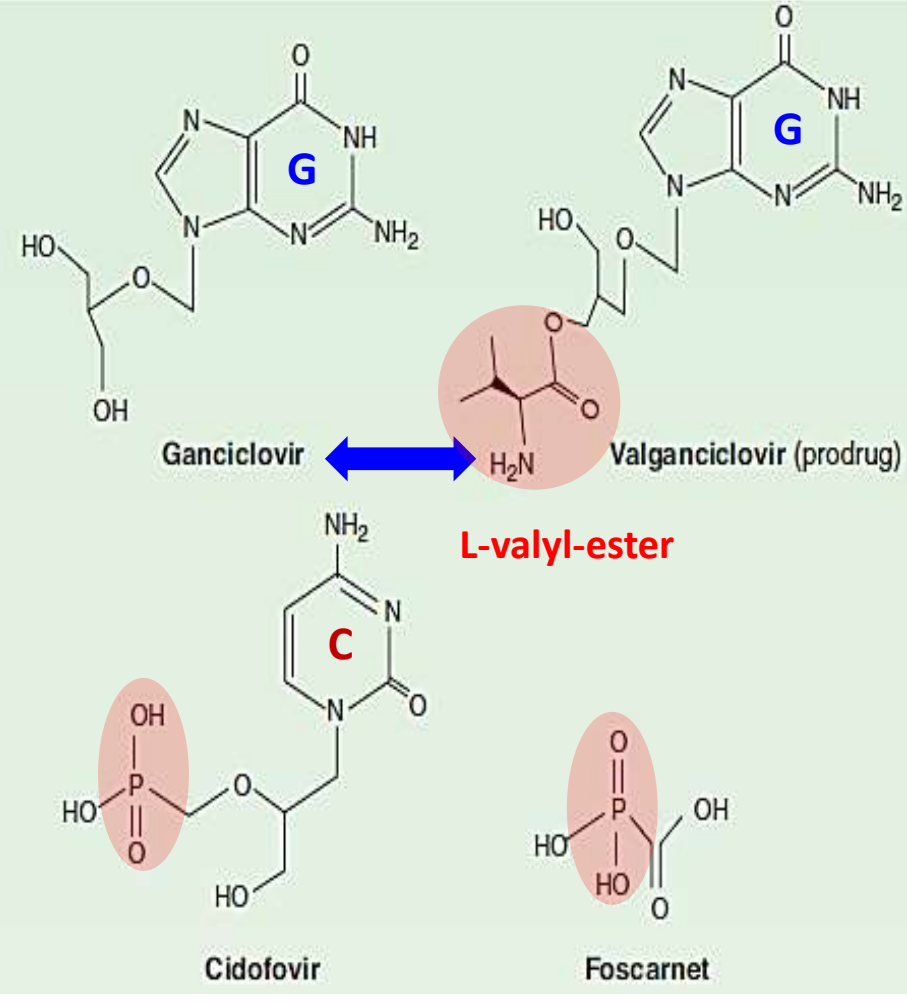

Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th, 2016

# Antiherpes agents

## For Herpesvirus




## For Cytomegalovirus (CMV)






Katzung BG: Basic and Clinical Pharmacology. 15th. 2021.

# Acyclovir (Zovirax®), Valacyclovir (Valtrex®)

- **Group:** Inhibition of viral genome replication (Anti-HSV nucleoside analog)
- **Mechanism:** Drugs are phosphorylated by viral kinases -> inhibit viral DNA-polymerase in virus-infected cells
- **Clinical uses:** HSV-1, HSV-2, VZV
- **ADR:**
  - Renal failure (IV), thrombocytopenia
  - Encephalopathic changes, dizziness, agitation
  - GI disturbance
- **Dosage form:**
  - Oral (F 15-20%, 3-5 times/day), IV, Topical (5% cream, 5 times/day)
  - $T_{1/2}$ 2-3 hr (adjust dose in renal impairment)
- **Valacyclovir**
  - is a prodrug of acyclovir (l-valyl ester) with greater oral bioavailability
  - Oral (F 60-70%, 2-3 times/day)

# Penciclovir (Denavir®), Famciclovir (Famvir®)

- **Group:** Inhibition of viral genome replication (Anti-HSV nucleoside analog)
- **Mechanism:** Drugs are phosphorylated by viral kinases -> inhibit viral DNA-polymerase in virus-infected cells
- **Clinical uses:** HSV-1, HSV-2, VZV
- **ADR:**
  - Erythema multiforme
  - GI disturbance, headache
- **Dosage form**
  - Topical (1% cream, q2hr)

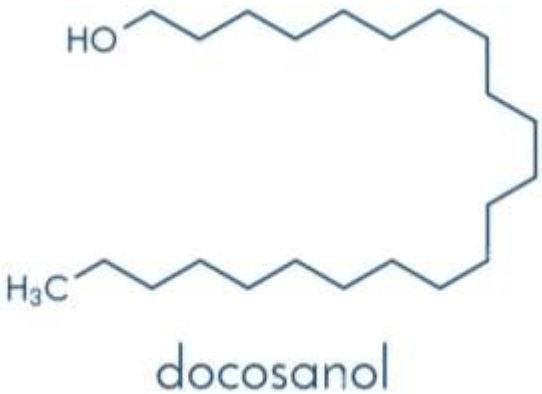
- **Famciclovir**
  - is a prodrug (diacetyl 6-deoxy) of penciclovir (active form)
  - Oral (F 70% , 1-3 times/day), $T_{1/2}$ 7-20 hr

# Trifluridine (Viroptic®)

- **Group:** Inhibition of viral genome replication (Anti-HSV nucleoside analog)
- **Mechanism:** Drugs are phosphorylated by host kinases* -> inhibit viral DNA-polymerase in virus-infected cells
- **Clinical uses:** HSV-1, HSV-2, HSV keratitis
- **ADR:**
  - Eye irritation, lacrimation, light intolerance
- **Consideration:**
  - Early anti-HSV drugs with increased toxicity than other agents
  - Trifluridine used as ophthalmic preparation (1% solution) for acyclovir-resistant HSV infection

# Docosanol (Abreva®)

- **Group:** Unknown mechanisms of action
- **Mechanism:** Unknown
- **Clinical uses:** HSV
- **ADR:**
  - Headache, application site reaction
- **Dosage form:** Topical (10% cream, q2hr)
- **Proposed mechanism:**
  - Docosanol is a saturated 22-carbon aliphatic alcohol
  - inhibits fusion between host cell plasma membrane and HSV envelope -> prevent viral entry into cells & viral replication



# Clinical uses of drugs for herpesviruses

- **Goals of Treatment: Relieve symptoms, shorten clinical course, prevent complications and recurrences, and decrease disease transmission**
- **Palliative and supportive therapy (Pain and discomfort: warm saline baths, analgesics, antipyretics, antipruritics)**

- ***VZV infections (chickenpox, shingles):***
  - **Oral in immunocompetent patients**
  - **IV in immunocompromised patients**
- ***HSV infections (genital herpes, herpes encephalitis, mucocutaneous herpes)***
- ***Prophylaxis:***
  - **who are to be treated with immunosuppressant drugs or radiotherapy**
  - **who are at high risk of herpesvirus infection owing to reactivation of a latent virus**
  - **who suffer from frequent recurrences of genital infection with herpes simplex virus**

# Clinical uses of drugs for herpesviruses

| Agent | Treatment of First Episode | Treatment of Recurrent Episodes | Suppression |
|---|---|---|---|
| **Genital Herpes** | | | |
| Acyclovir, oral[1] | 400 mg tid or 200 mg 5 times daily × 7–10 days | 800 mg tid × 2 days or 800 mg bid × 5 days or 400 mg tid × 5 days | 400–800 mg bid-tid[2,3] |
| Famciclovir, oral[1] | 250 mg tid × 7–10 days | 1000 mg bid × 1 day or 125 mg bid × 5 days or 500 mg once then 250 mg bid × 2 days[2] | 250–500 mg bid[2,3] |
| Valacyclovir, oral[1] | 1000 mg bid × 7-10 days | 500 mg bid × 3 days or 1 g qd × 5 days | 500–1000 mg qd–bid[2] |

Katzung BG: Basic and Clinical Pharmacology. 15th. 2021.

# Clinical uses of drugs for herpesviruses

| Agent | Treatment of First Episode | Treatment of Recurrent Episodes | Suppression |
|---|---|---|---|
| **Orolabial herpes** | | | |
| Acyclovir, oral[1] | 400 mg tid × 7–10 days<br>or 200 mg 5 times daily | 200–400 mg 5 times daily × 5 days | 400–800 mg bid–tid[2] |
| Famciclovir, oral[1] | 500 mg tid × 7–10 days | 1500 mg once or 750 mg bid | 500 mg bid |
| Valacyclovir, oral[1] | 1 g bid × 7–10 days | 2 g bid × 1 day | 500–1000 mg qd |
| Acyclovir, topical (5% cream) | | 5 times daily × 4 days | |
| Acyclovir, mucoadhesive buccal tablet | | Once during prodrome | |
| Docosanol, topical (10% cream) | | 5 times daily | |
| Penciclovir, topical (1% cream) | | Every 2 h while awake | |

Katzung BG: Basic and Clinical Pharmacology. 15th. 2021.

# Clinical uses of drugs for herpesviruses

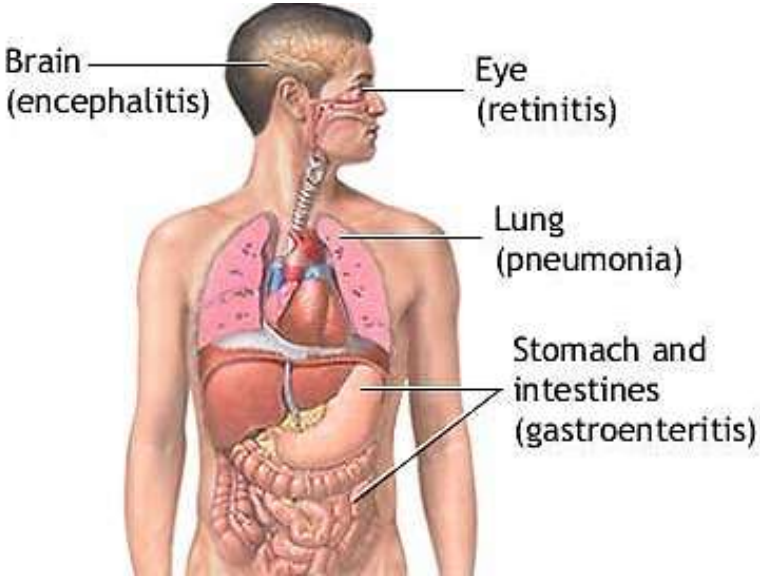
| Agent | Treatment of First Episode | Treatment of Recurrent Episodes | Suppression |
|---|---|---|---|
| **Varicella infection, treatment** | | | |
| Acyclovir, oral[1] | 20 mg/kg (maximum 800 mg) qid × 5 days | | |
| Valacyclovir, oral[1] | 20 mg/kg (maximum, 1 g) tid × 5 days | | |
| **Zoster infection, treatment** | | | |
| Acyclovir, oral[1] | 800 mg 5 times daily × 7–10 days | | |
| Famciclovir, oral[1] | 500 mg tid × 7 days | | |
| Valacyclovir, oral[1] | 1 g tid × 7 days | | |
| **Severe VZV infection or VZV infection in the immunocompromised host, treatment** | | | |
| Acyclovir, IV[1] | 10–15 mg/kg q8h × ≥7 days | | |
| **Acyclovir-resistant HSV or VZV infection, treatment** | | | |
| Foscarnet, IV[1] | 40–60 mg/kg q8h until healed[2] | | |

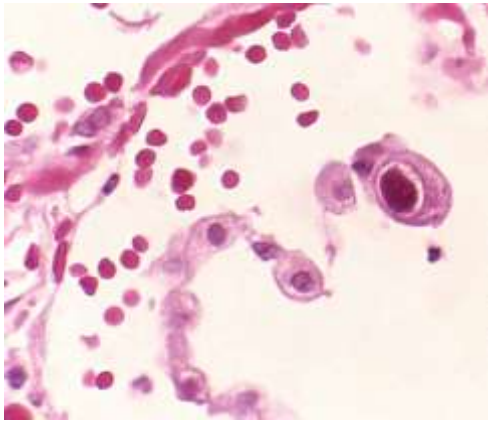
Katzung BG: Basic and Clinical Pharmacology. 15th. 2021.

# Antiviral Drugs for Cytomegalovirus (CMV) Infection

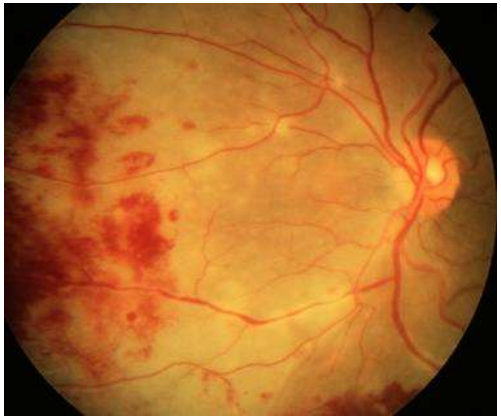
# Cytomegalovirus (CMV)

- CMV is a common virus in the same family as herpesvirus
- CMV is spread by direct contact of body fluids, such as saliva, blood, urine, semen, vaginal fluids, and breast milk
- CMV infections occur in the setting of advanced immunosuppression and are typically due to reactivation of latent infection
- Disease: (HIV patient, $CD_4$ <50 cells/$mm^3$)
  - Common: CMV retinitis
  - Others: hepatitis, colitis, pneumonia, encephalitis



Owl eye

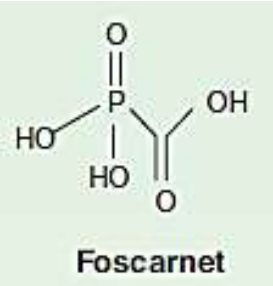


# Ganciclovir (Cytovene®), Valganciclovir (Valcyte®)

- **Group:** Inhibition of viral genome replication (Anti-HSV nucleoside analog)
- **Mechanism:** Drugs are phosphorylated by viral kinases -> inhibit viral DNA-polymerase in virus-infected cells
- **Clinical uses:** CMV retinitis
- **ADR:**
  - Neutropenia, thrombocytopenia, anemia
  - Fever, phlebitis
- **Dosage form:** IV
- **Contraindication:** Severe neutropenia, severe thrombocytopenia
- **Valganciclovir**
  - is a prodrug of ganciclovir (l-valyl ester) with greater oral bioavailability
  - Oral (F 60% , 1 time/day)

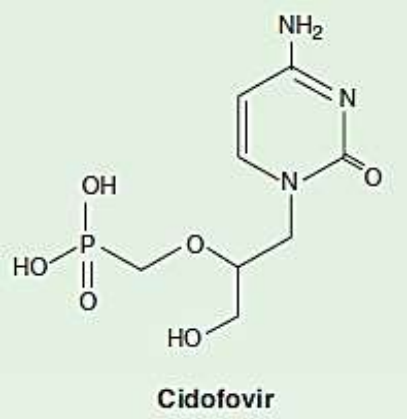
# Foscarnet (Foscavir®)

- **Group:** Inhibition of viral genome replication (Non-nucleoside DNA polymerase inhibitors)
- **Mechanism:** Inhibit viral DNA polymerase directly by mimicking pyrophosphate product of DNA polymerase reaction
- **Clinical uses:** CMV retinitis
- **ADR:**
  - Nephrotoxicity (dose-dependent)
  - Electrolyte imbalance (↓/↑ $Ca^{2+}$, ↓/↑ $PO_4^{3-}$, ↓ $K^+$, ↓ $Mg^{2+}$)
  - CNS: headache, hallucination, seizure
  - Anemia, fever, GI disturbance
- **Dosage form:** IV
- **Contraindication:** Concurrent use of nephrotoxicity drugs (amphotericinB, aminoglycosides), imipenem (risk of seizure)
- **Consideration:**
  - Renal impairment is the major dose-limiting toxicity
  - Foscarnet is used for CMV infections that are resistant to antiherpesvirus nucleoside analogues



# Cidofovir (Vistide®)

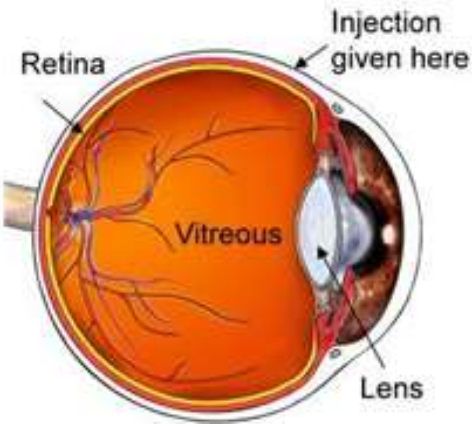
- **Group:** Inhibition of viral genome replication (Anti-HSV nucleoside analog)
- **Mechanism:** Cidofovir is phosphorylated by cellular enzymes** -> inhibit CMV DNA-polymerase




- **Clinical uses:** CMV retinitis
- **ADR:**
  - Nephrotoxicity (dose-dependent)
  - Neutropenia, metabolic acidosis, decreased intraocular pressure
  - GI disturbance, headache, rash
- **Dosage form:** IV, Long $T_{1/2}$, once weekly
- **Contraindication:** renal insufficiency, concomitant use with nephrotoxic agents

# Fomivirsen (Vitravene®)

- **Group:** Unknown mechanisms of action
- **Mechanism:** Unknown
- **Clinical uses:** CMV retinitis (2nd-line)
- **ADR:**
  - Inflammatory disorders of eyes, transiently elevated intraocular pressure
- **Contraindication:** IV or cidofovir within 2-4 weeks (increase risk of ocular inflammation)
- **Consideration:**
  - Fomivirsen was designed as an antisense nucleotide, but mechanism is uncertain
  - Administered intravitreally

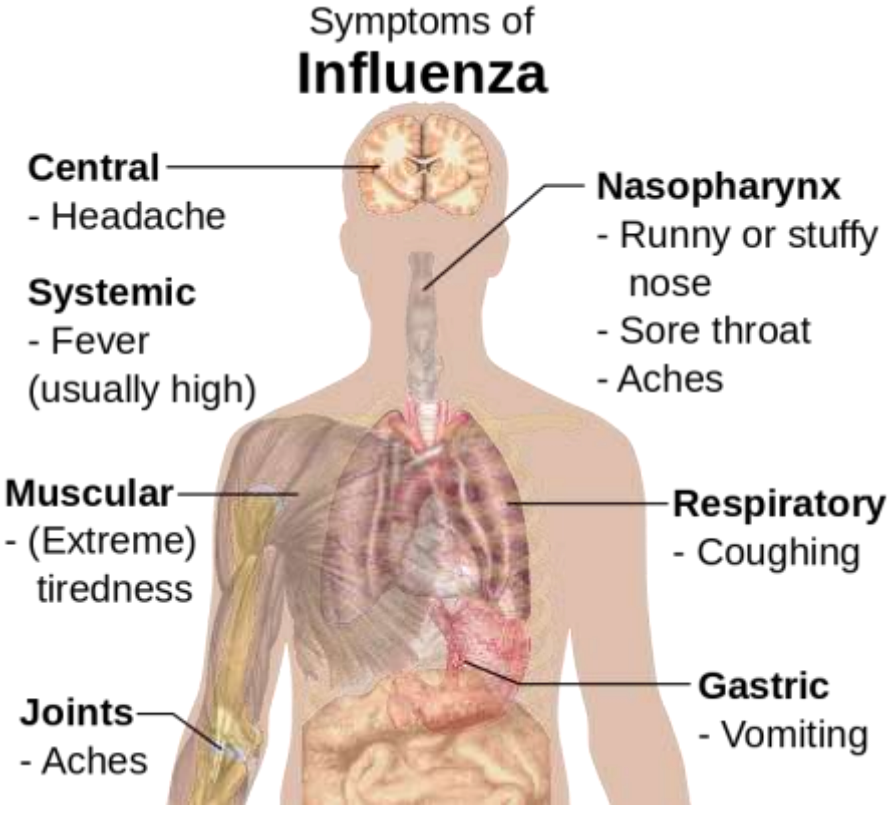


# Clinical uses of drugs for CMV

| Agent | Route of Administration | Use | Recommended Adult Dosage |
|---|---|---|---|
| Valganciclovir[1] | Oral | CMV retinitis treatment | Induction: 900 mg bid × 21 days |
| | | | Maintenance: 900 mg daily |
| | Oral | CMV prophylaxis (transplant patients) | 900 mg daily |
| Ganciclovir[1] | Intravenous | CMV retinitis treatment | Induction: 5 mg/kg q12h × 14–21 days |
| | | | Maintenance: 5 mg/kg/d or 6 mg/kg five times per week |
| Foscarnet[1] | Intravenous | CMV retinitis treatment | Induction: 60 mg/kg q8h or 90 mg/kg q12h × 14–21 days |
| | | | Maintenance: 90–120 mg/kg/d |
| Cidofovir[1] | Intravenous | CMV retinitis treatment | Induction: 5 mg/kg/wk × 2 weeks |
| | | | Maintenance: 5 mg/kg every week |

Katzung BG: Basic and Clinical Pharmacology. 15th. 2021.

# Antiviral Drugs for Influenza Virus Infection



# Influenza virus

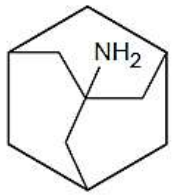
- Influenza A and B viruses are 2 types that cause disease in humans
  - Influenza A viruses (H3N2 & H1N1): Regular, seasonal epidemics of the flu
  - Influenza B viruses: Sporadic outbreaks
- Primary route of transmission: person-to-person via inhalation of respiratory droplets (coughs or sneezes)
- Symptoms:
  - Factor: age, immunocompetence, viral characteristics, smoking, comorbidities, pregnancy, etc
  - Classical sign: rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, rhinitis
  - Incubation period: 1-7 days (average 2 days), resolve in 3-7 days
- Diagnosis:
  - History & symptoms
  - Gold standard for diagnosis of influenza is viral culture

# Influenza virus

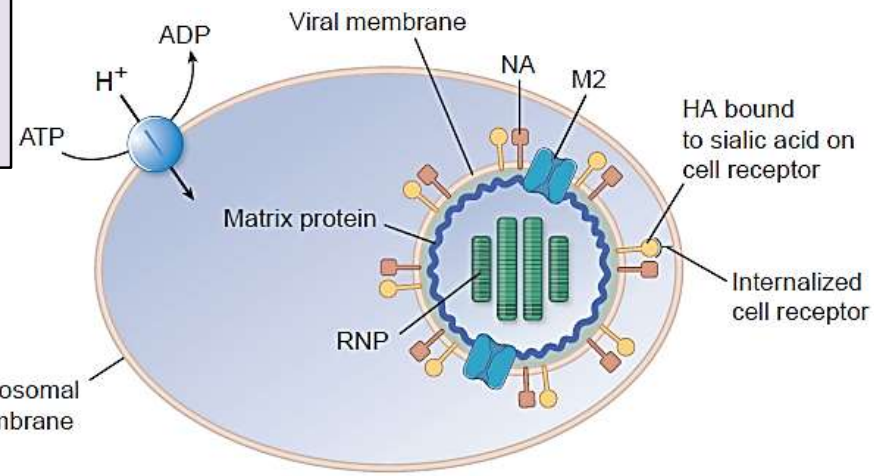
- **Prevention**
  - **The best way is to prevent infection through vaccination**
  - **Infection control measures: hand hygiene, respiratory etiquette (cover cough and throw tissues away), contact avoidance**
- **Treatment:**
  - **Goals of Therapy**
    - **1) control symptoms**
    - **2) prevent complications**
    - **3) decrease work and/or school absenteeism**
    - **4) prevent the spread of infection**
  - **Antiviral drugs are most effective if started within 48 hours of the onset of illness**
  - **Adjunct agents (such as acetaminophen for fever, antihistamine for rhinitis) may be used concomitantly with antiviral drugs**

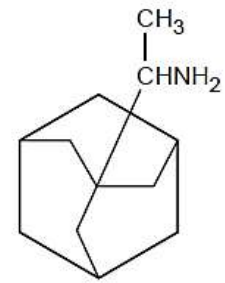
# I. M2 proton channel inhibitors

(Inhibition of viral uncoating)



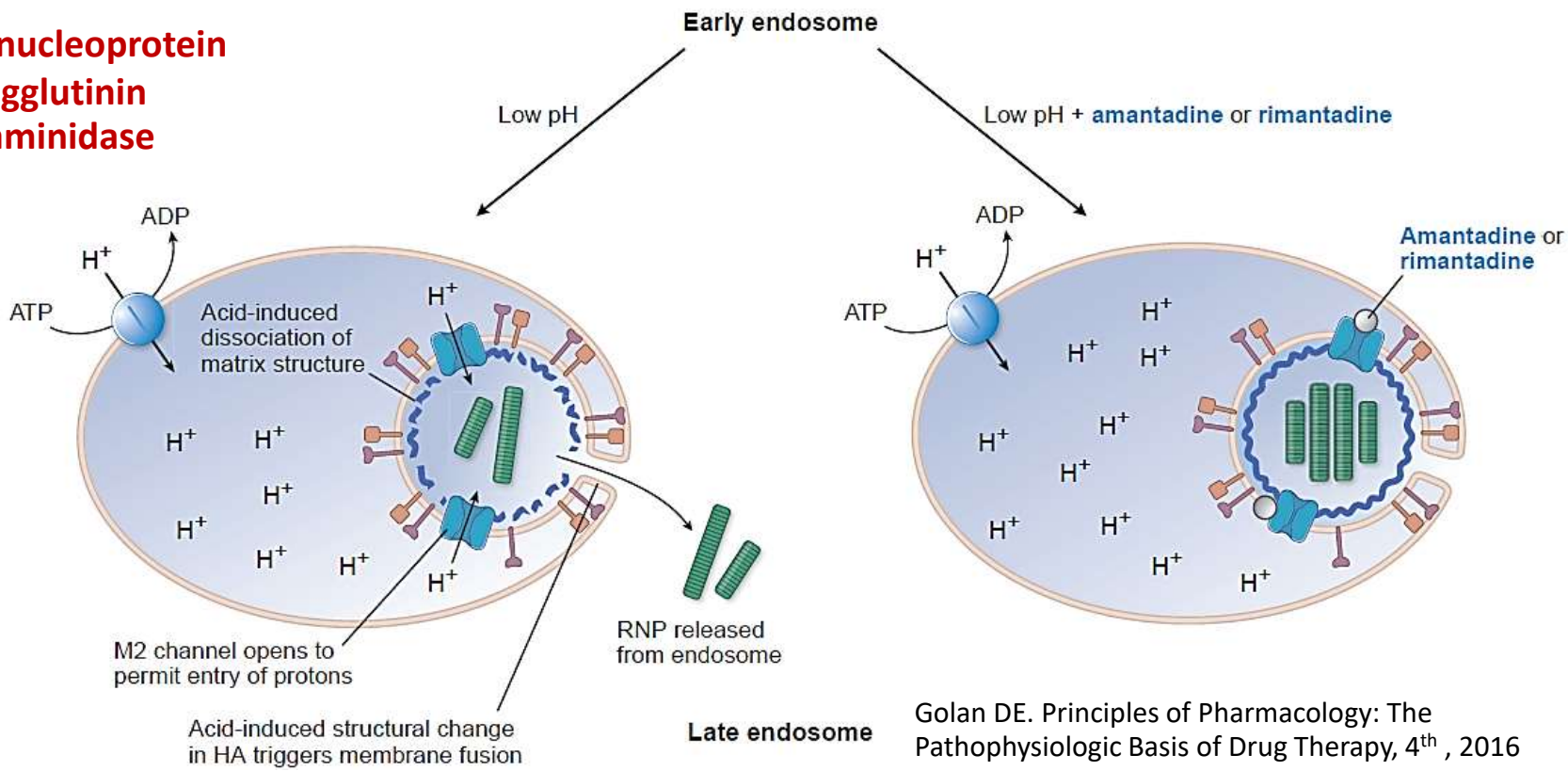

Amantadine




Rimantadine

**RNP; ribonucleoprotein**
**HA; hemagglutinin**
**NA; neuraminidase**



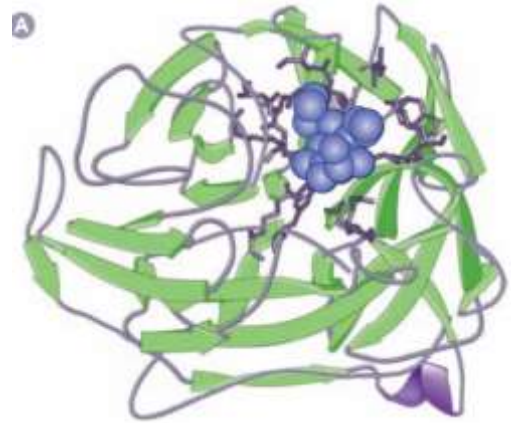

Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th , 2016

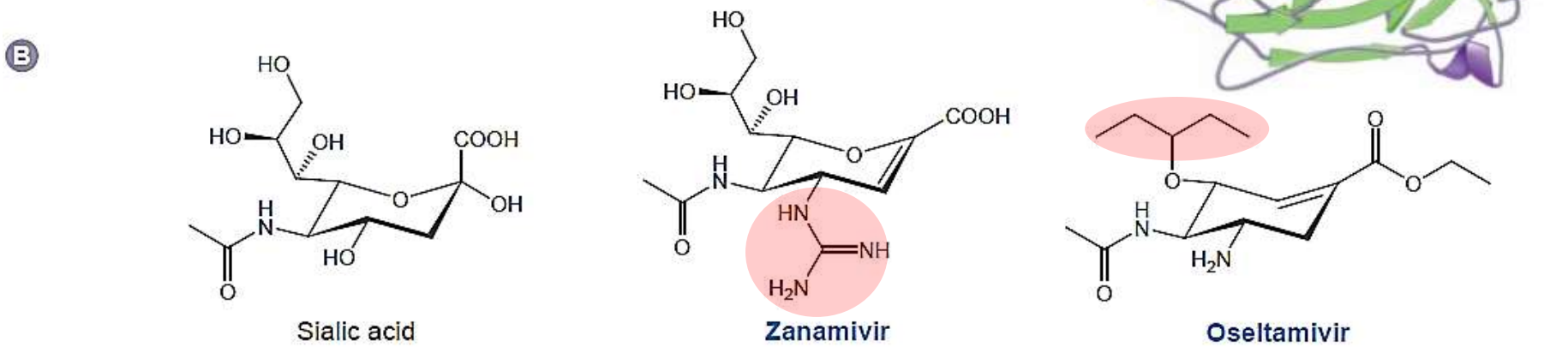
# Amantadine (Symmetrel®), Rimantadine (Flumadine®)

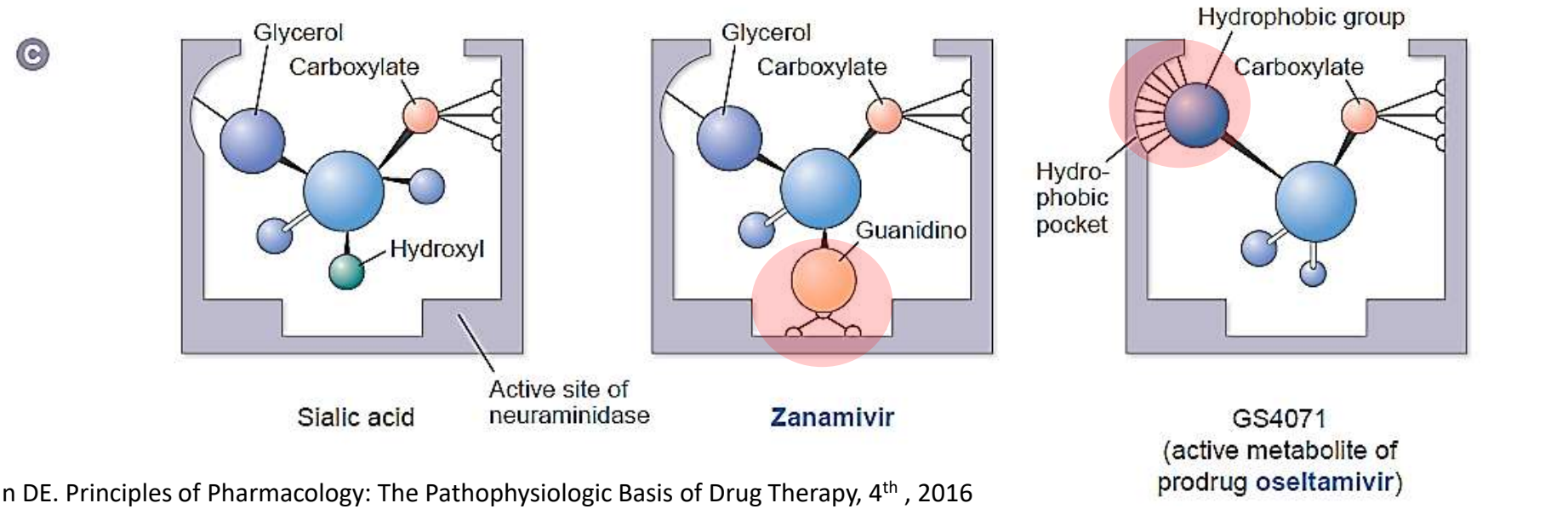
- **Group:** M2 proton channel inhibitors (Inhibitors of viral uncoating)
- **Mechanism:** Block $M_2$, a proton channel that acidifies interior of virus (acidification is necessary for dissociation of viral matrix protein from viral ribonucleoprotein)
- **Clinical uses:** Influenza A
- **ADR:**
  - Neuroleptic malignant syndrome (NMS)
  - Exacerbation of mental disorders, confusion, insomnia, hallucination
  - Orthostatic hypotension, peripheral edema, GI disturbance
- **Consideration:**
  - Rimantadine cause fewer neurological effect than amantadine
  - The use of these drugs has been supplanted by neuraminidase inhibitors

# II. Neuraminidase inhibitors
(Inhibition of viral release)

**Sialic acid bound to influenza A virus neuraminidase**



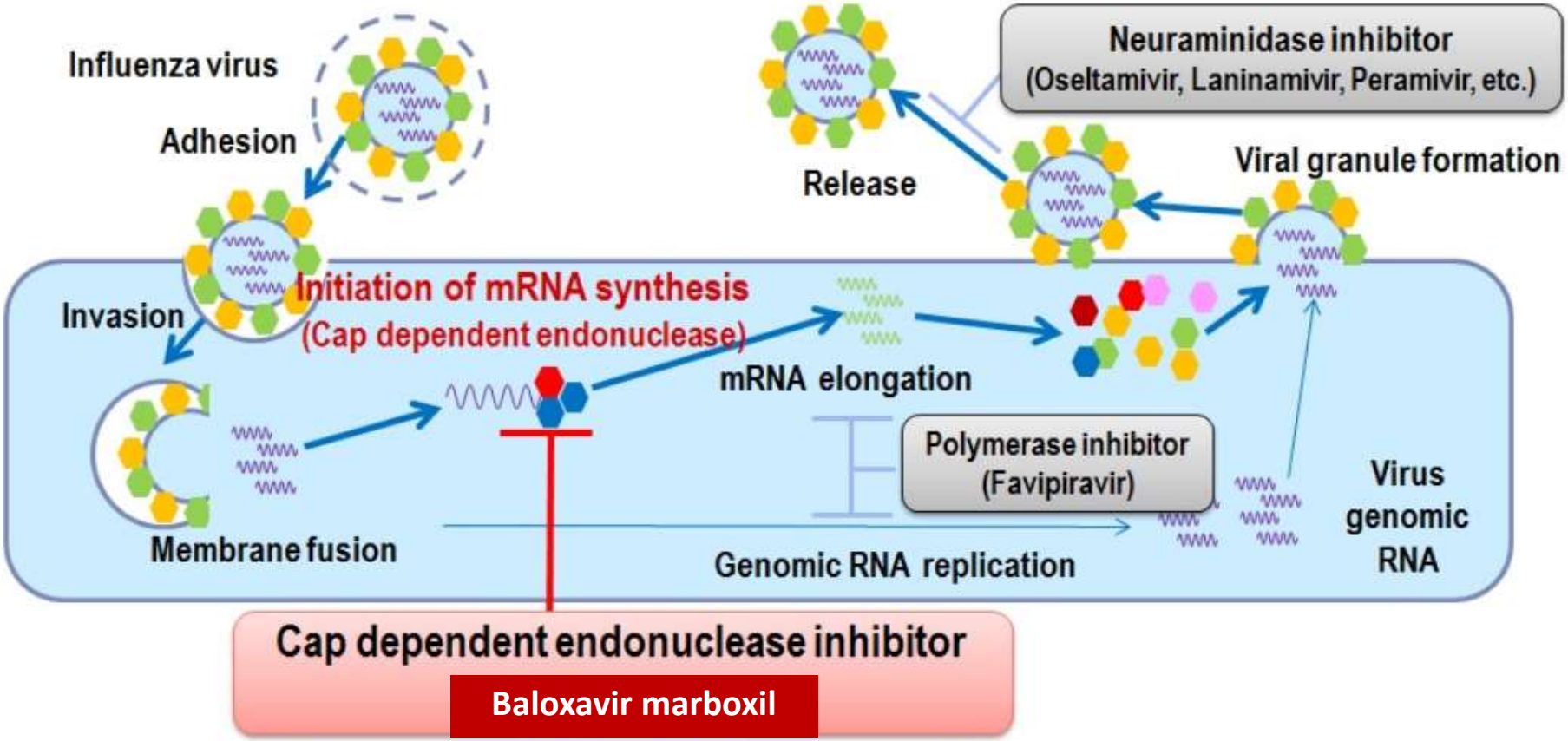

Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th , 2016

# Zanamivir (Relenza®), Oseltamivir (Tamiflu®), Peramivir (Rapivab®)

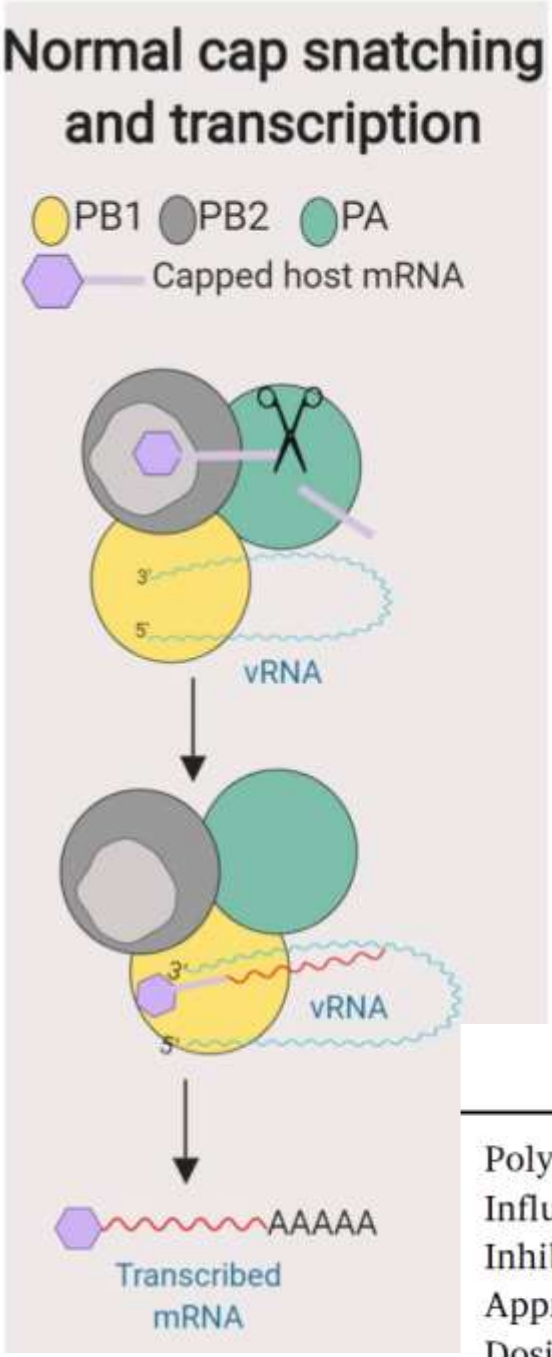
- **Group: Neuraminidase inhibitors (Inhibition of viral release)**
- **Mechanism: Inhibit influenza virus neuraminidase, causing newly synthesized virions to remain attached to host cells**
- **Clinical uses: Influenza A & B**
- **ADR:**
  - **Bronchospasm, respiratory depression**
  - **GI disturbance, headache, nasal symptoms**
- **Consideration:**
  - **Zanamivir : inhaler, Oseltamivir : oral, Peramivir : IV**
  - **Oseltamivir & Zanamivir is approved for both prophylaxis and treatment**
  - **Peramivir is approved only for treatment**

# III. Viral polymerase complex inhibitor

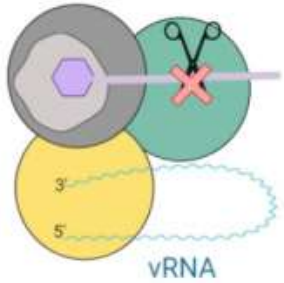
(Inhibition of viral replication)




http://www.shionogi.co.jp/en/ir/pdf/e_p151030.pdf

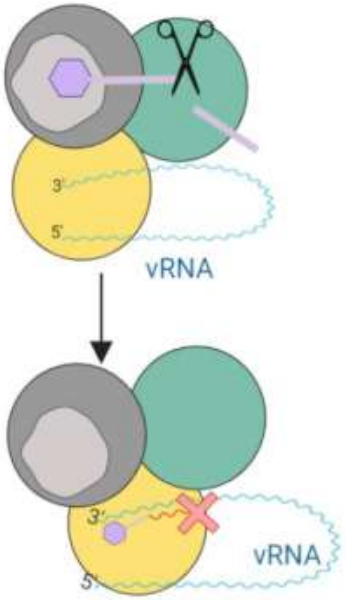



**Baloxavir**




Inhibition of endonuclease activity

**Favipiravir**




Inhibition of correct mRNA elongation

**Polymerase complex** of influenza viruses is a heterotrimer composed of 3 protein subunits:

- Polymerase basic protein 1 (PB1)
- Polymerase basic protein 2 (PB2)
- Polymerase acidic protein (PA) (by cap-dependent endonuclease)

| | Baloxavir | Favipiravir |
|---|---|---|
| Polymerase target | PA | PB1 |
| Influenza specificity | A, B, & C | A, B & C |
| Inhibitory for non-influenza viruses | No | Yes |
| Approved for influenza use | Japan, USA | Japan (but restricted) |
| Dosing route | Oral | Oral |

Antiviral Res. 2019;169:104545.

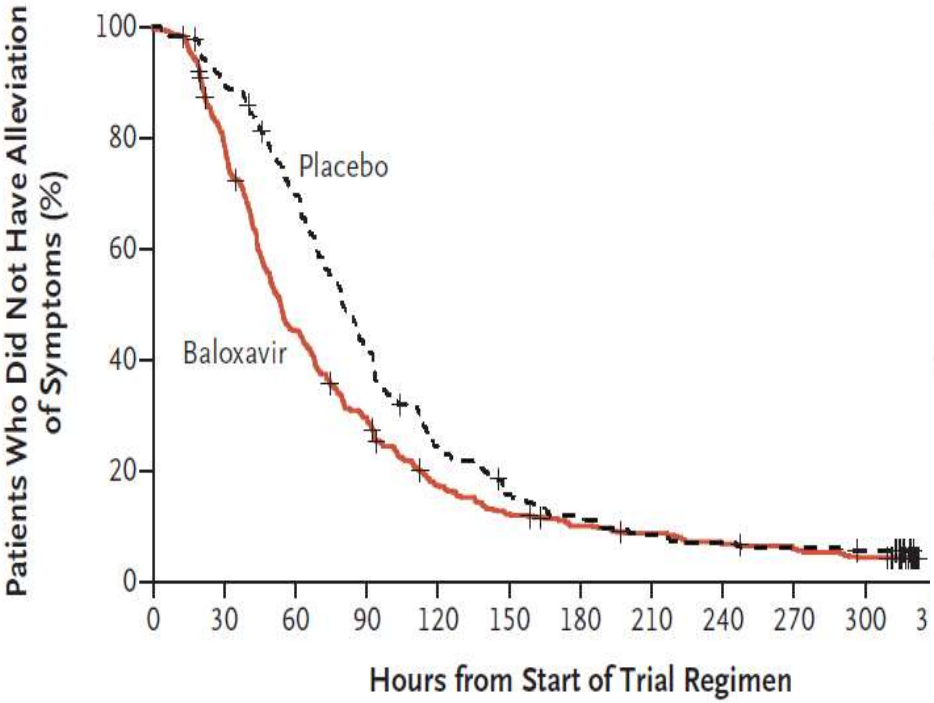
# Baloxavir marboxil (Xofluza®)

- **Group:** **Cap-dependent endonuclease (Inhibition of viral replication)**
- **Mechanism:** **Inhibit cap-dependent endonuclease,** **an enzyme used in "cap snatching" by viral polymerase complex (required for initiation of influenza mRNA synthesis)**
- **Clinical uses:** **Influenza A & B**
- **ADR:**
  - **Diarrhea, bronchitis, headache, nausea**
- **Consideration:**
  - **Median time to $C_{max}$ 4 h; mean elimination half-life 96 h**
  - **Prodrug: Baloxavir marboxil (BXM) → Active: Baloxavir acid (BXA)**
  - **Adult dose: 20, 40 mg, 2 tablets- Once (** Single dose **)**

# Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

**Time to Alleviation of Influenza Symptoms**

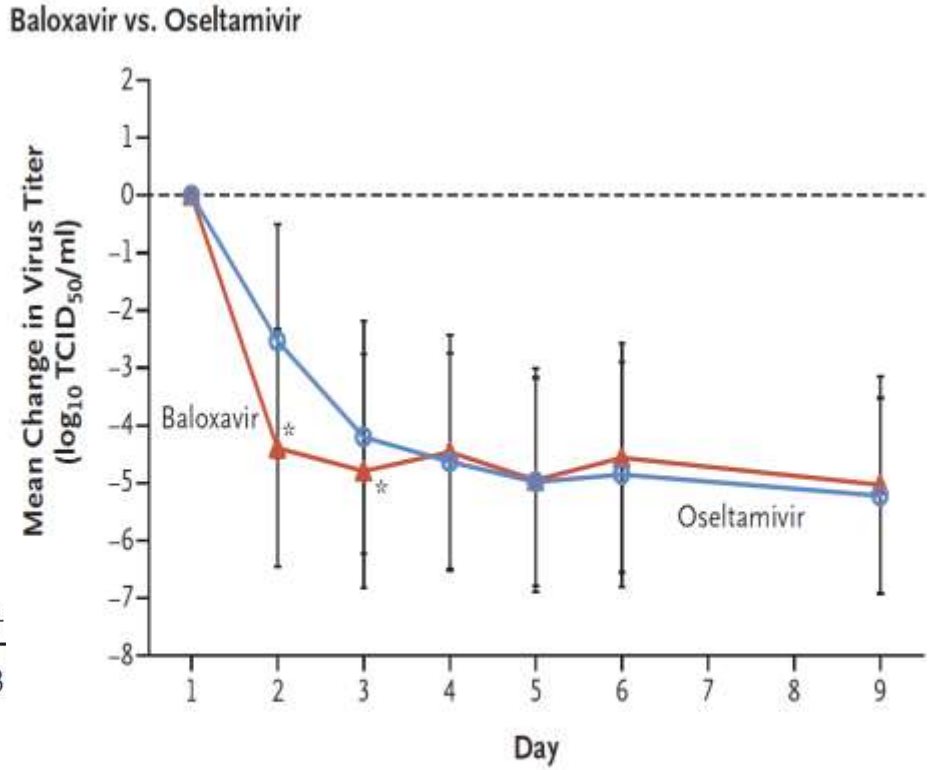
Baloxavir (N=455) versus Placebo (N=230)




Median time to alleviation of symptoms was 26.5 hours shorter in the baloxavir group

**Change from Baseline in Viral Load over Time**

Baloxavir (N=352) versus Oseltamivir (N=359)

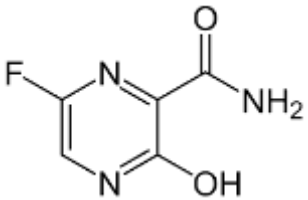




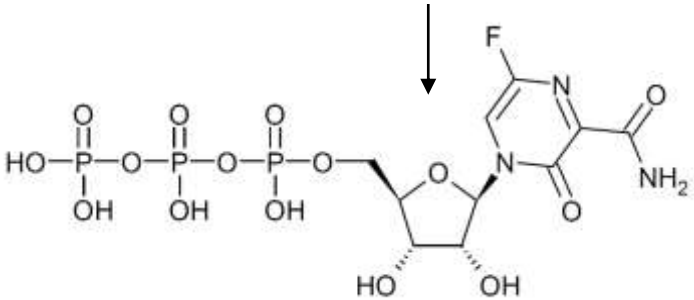

Hayden FG, et al. N Engl J Med. 2018;379(10):913-923.

# Favipiravir (Avigan®)

- **Group: Inhibition of viral replication (nucleoside analog)**
- **Mechanism: Inhibits RNA-dependent RNA polymerases**
- **Clinical uses: Influenza A & B**
- **ADR:**
  - **Diarrhea, nausea, vomiting, ↑ uric acid**
  - **Teratogenicity**




**Favipiravir**




**Favipiravir-RTP (Active form)**

- **Consideration:**
  - **Oral and IV**
  - **Prodrug: Favipiravir -> Active form: Favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP) -> mimics both A & G**
  - **Broad spectrum for RNA viruses: influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus, flaviviruses, arenaviruses, bunyaviruses, alphaviruses**

# PK of antivirals for influenza

| | AMANTADINE | RIMANTADINE | ZANAMIVIR | OSELTAMIVIR | PERAMIVIR | BALOXAVIR |
|---|---|---|---|---|---|---|
| Spectrum[f] | A | A | A, B | A, B | A, B | A, B |
| Route/formulations | Oral (tablet/capsule/syrup) | Oral (tablet/syrup) | Inhaled (powder)<br>Intravenous[a] | Oral (capsule/syrup)<br>Intravenous[a] | Intravenous | Oral (tablet/sus |
| Oral bioavailability | >90% | >90% | <5%[b] | 80%[c] | Not applicable | >95% |
| Effect of meals on AUC | Negligible | Negligible | Not applicable | Negligible | Not applicable | ↓ 36% |
| Elimination $t_{1/2}$, h | 12–18 | 24–36 | 2.5–5 | 6–10[c] | 20 | 79 |
| Protein binding, % | 67% | 40% | <10% | 3%[c] | <30% | 93% |
| Metabolism, % | <10% | ~75% | Negligible | Negligible | Negligible | 80% |
| Renal excretion[e] | >90% | ~25% | 100% | 95%[c] | 90% | Negligible |
| Dose adjustments | $Cl_{cr} \leq 50$<br>Age ≥ 65 years | $Cl_{cr} \leq 10$<br>Age ≥ 65 years | None[d] | $Cl_{cr} \leq 30$ | $Cl_{cr} \leq 50$ | < 80 kg; 40 mg<br>≥80 kg; 80 mg |



Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Antiviral susceptibility of influenza viruses

**TABLE 127-4 Antiviral Susceptibilities of Circulating Viruses[53]**

| | Baloxavir | Oseltamivir | Zanamivir | Peramivir | Adamantanes |
|---|---|---|---|---|---|
| Variant influenza A (H3N2), 2015 | Susceptible | Susceptible | Susceptible | Susceptible | Resistant |
| Novel influenza A (H1N1) | Susceptible | Susceptible[a] | Susceptible | Susceptible[a] | Resistant |
| Seasonal A (H3N2) | Susceptible | Susceptible | Susceptible | Susceptible | Resistant |
| Influenza B | Susceptible | Susceptible | Susceptible | Susceptible | Resistant |
| Avian influenza (H5N1) | Susceptible | Susceptible | Susceptible | Susceptible | Variable |

**Adamantanes: amantadine, rimantadine**

DiPiro JT, et al. Pharmacotherapy: A Pathophysiologic Approach, 11th, 2020

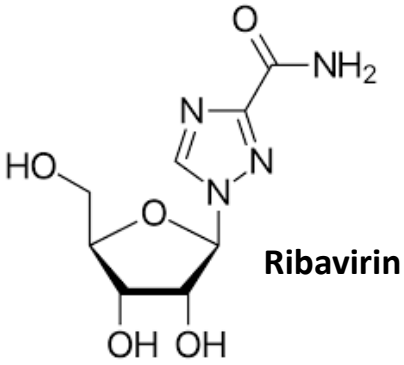
# Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis

| Drug | Adult Treatment | Adult Prophylaxis |
|---|---|---|
| Baloxavir | 40-80 kg: 40 mg, Once<br>> 80 kg: 80 mg, Once | None |
| Oseltamivir | 75-mg capsule twice daily x 5 days | 75-mg capsule daily x 10 days |
| Zanamivir | 10 mg (2 inhalations) twice daily × 5 days | 10 mg (2 inhalations) daily × 10 days |
| Rimantadine | 200 mg/day in 1-2 doses × 7 days | 200 mg/day in 1-2 doses |
| Amantadine | 200 mg/day in 1-2 doses until 24-48 hours after symptom resolution | Same as treatment doses |

DiPiro JT, et al. Pharmacotherapy: A Pathophysiologic Approach, 11th, 2020

# Other Antiviral Drugs

# Ribavirin (Rebetol®)



Ribavirin

- **Group:** Inhibition of viral replication (nucleoside analog)
- **Mechanism:** 2 proposed mechanisms
  - Inhibit inosine monophosphate dehydrogenase -> ↓ cellular GTP levels
  - Inhibit viral RNA polymerases -> mimic G
- **Clinical uses:** Respiratory syncytial virus (RSV), HCV (in combination with interferon-α)
- **ADR:**
  - Bradyarrhythmia, hypotension
  - Pancreatitis, hepatotocixity
  - Hemolytic anemia, thrombocytopenia, bacterial infection, suicide
  - Rash, GI disturbance, headache, conjunctivitis, fatigue
- **Contraindication:** cardiac diseases, Crcl < 50 mL/min, severe hepatic impairment

# Palivizumab (Synagis®)

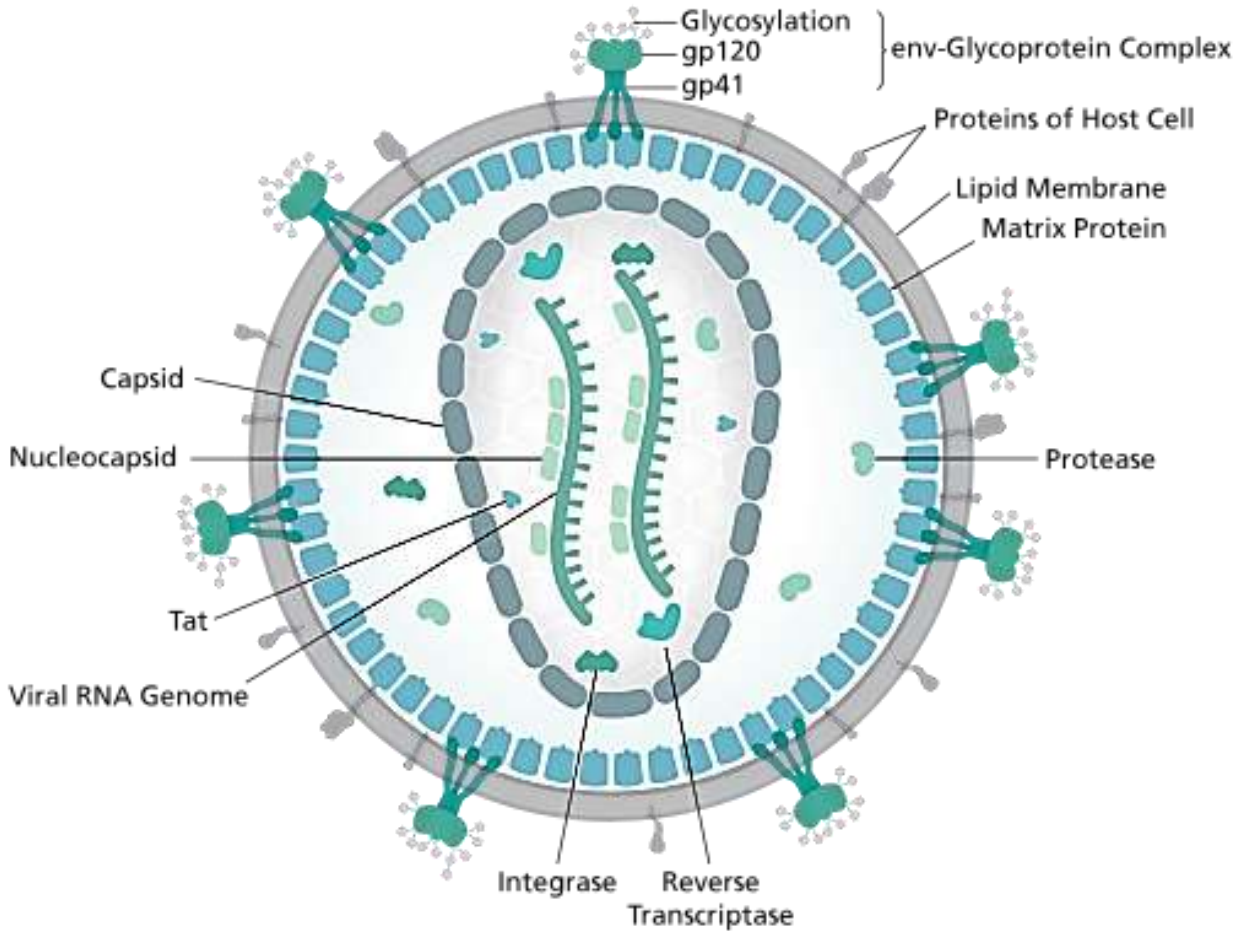
- **Group: -**
- **Mechanism: Palivizumab is a humanized monoclonal antibody directed against an epitope in A antigen site on F surface protein of RSV**
- **Clinical uses: RSV infection in high-risk infants and children (premature infants)**
- **ADR:**
  - **Upper respiratory tract infection, fever, rhinitis, cough, otitis media**
  - **Rash, diarrhea, vomiting, elevation in serum aminotransferase levels**
- **Dosage: IM**

# Imiquimod (Aldara®)

- **Group:** Drugs that modulate immune system
- **Mechanism:** Interact with toll-like receptors (TLR7 agonist) to boost innate immunity, including secretion of interferons
- **Clinical uses:** human papilloma virus (HPV), basal cell carcinoma, Actinic keratosis, genital wart (condyloma acuminatum)
- **ADR:**
  - Skin irritation (erythema, superficial erosion/crusting), burning sensation
- **Dosage:**
  - Topical (5% cream, 3 times/week, overnight), Wash hands before and after application

# Antiviral Drugs for Retrovirus Infection

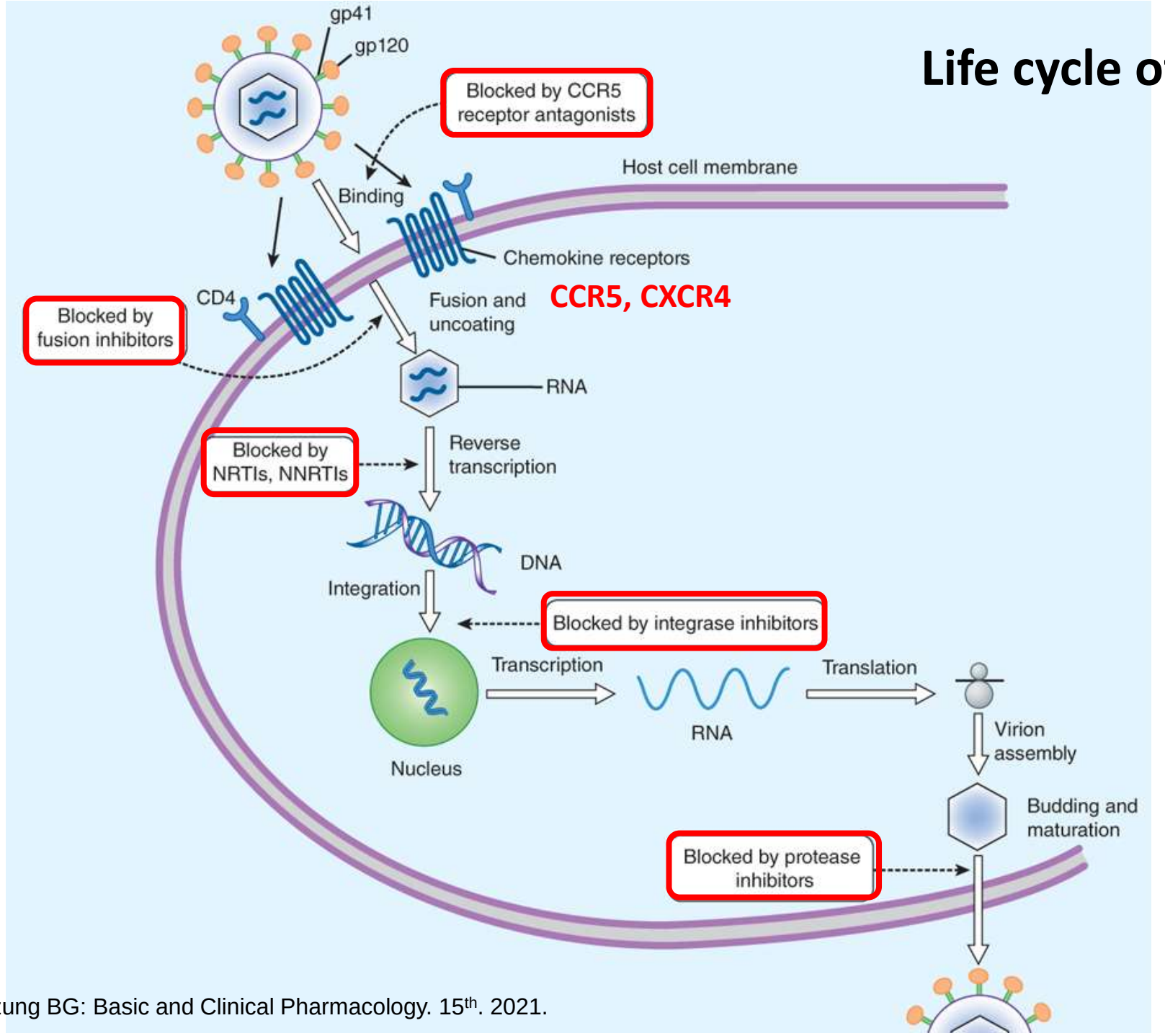
## *Antiretroviral therapy (ART)*



# Human immunodeficiency virus (HIV) infection

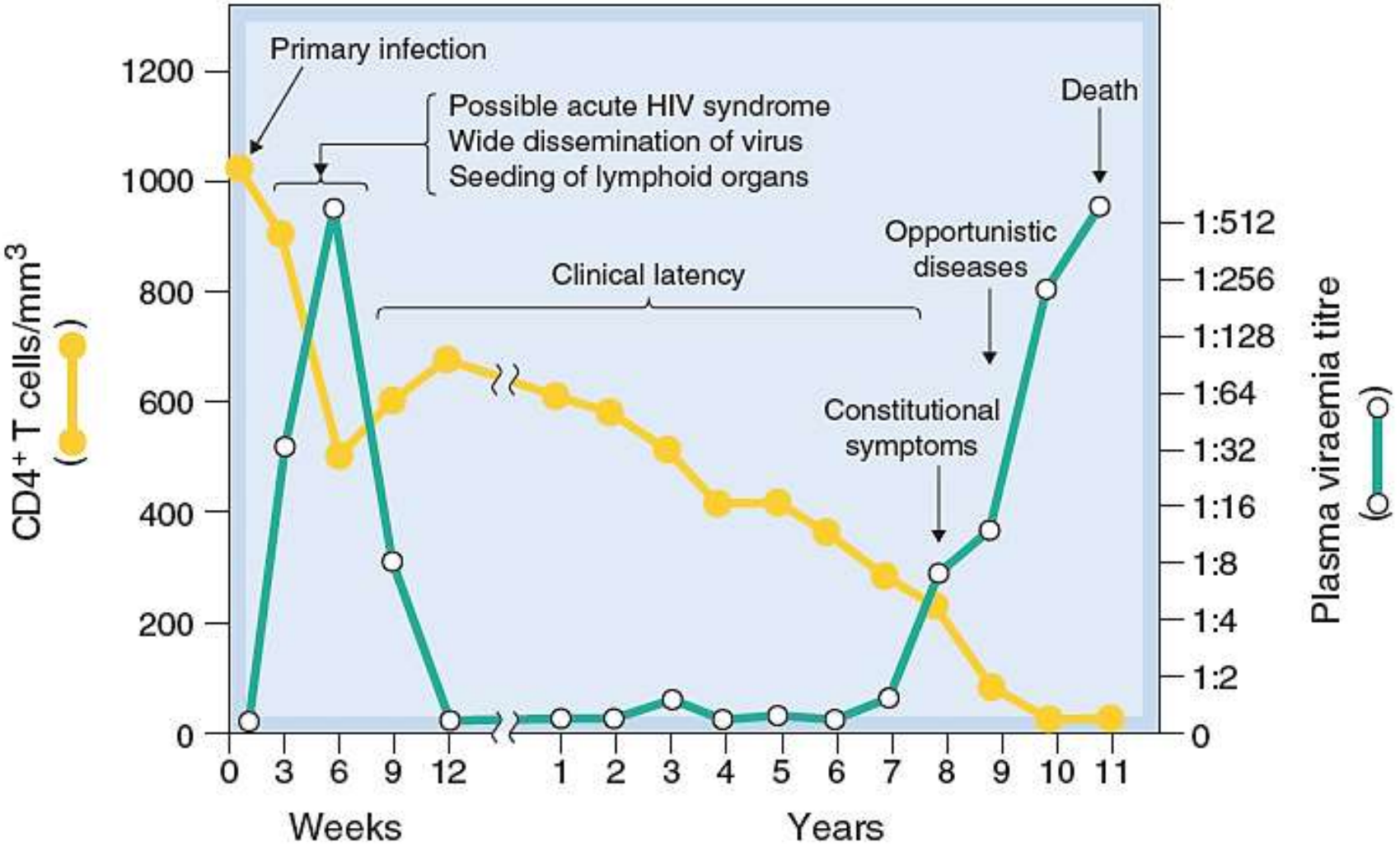
- **Route:**
  - 3 primary modes (sexual, parenteral, perinatal)
  - Sexual intercourse: anal (0.5-3% per sexual contact) & vaginal intercourse
  - Condom use reduces the risk of transmission by ~20-fold
- **Clinical presentations**: vary
  - Fever, sore throat, fatigue, weight loss, and myalgia
  - 40%-80% of patients will also exhibit maculopapular rash (trunk)
  - Diarrhea, nausea, and vomiting
  - Lymphadenopathy, night sweats
  - Aseptic meningitis (fever, headache, photophobia, stiff neck) -> ¼ of case
- **Goal of Treatment:**
  - Decrease morbidity and mortality
  - Improve quality of life
  - Restore and preserve immune function
  - Prevent further transmission through maximum suppression of HIV replication (HIV RNA level that is undetectable)

# Life cycle of HIV



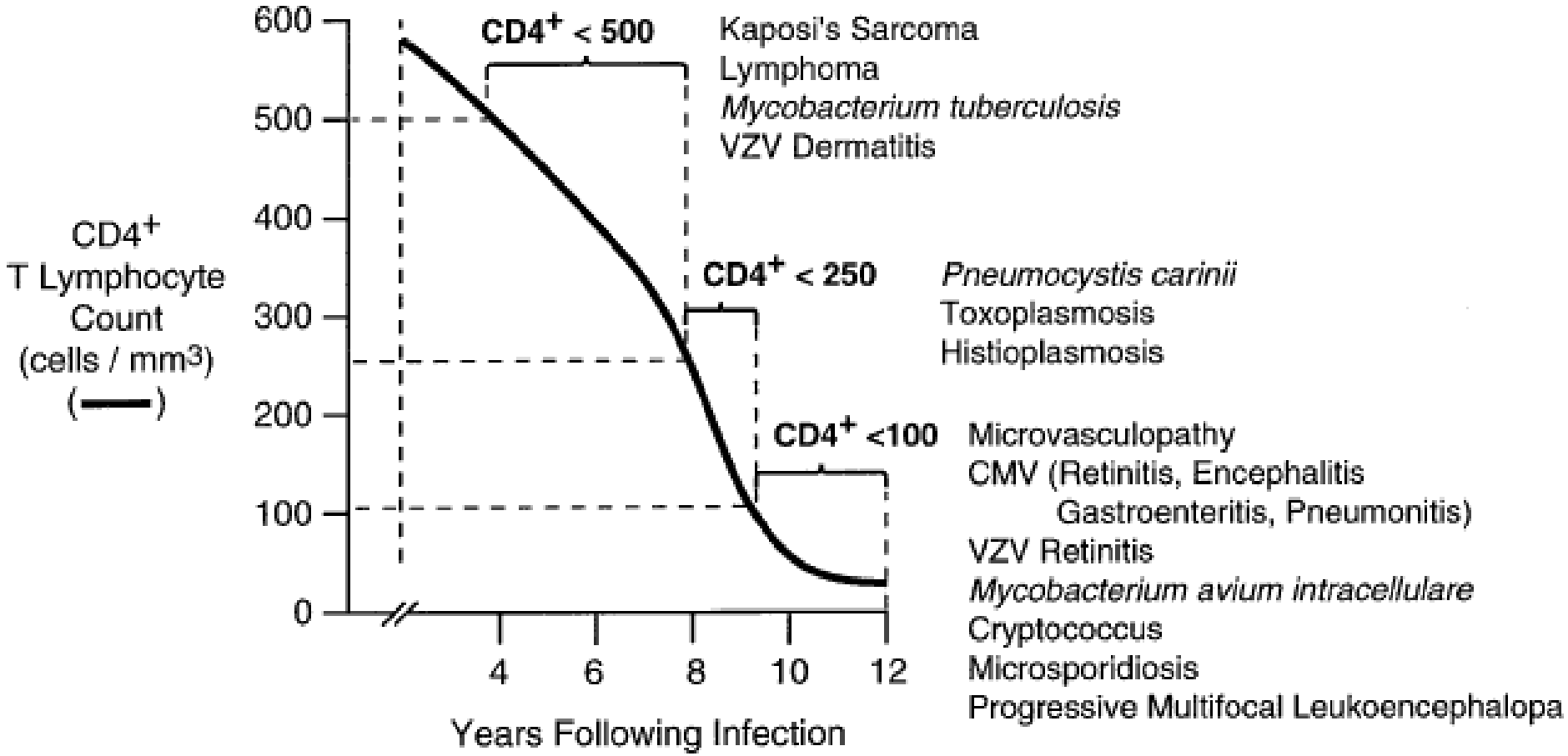

Katzung BG: Basic and Clinical Pharmacology. 15th. 2021.

# Course of untreated HIV infection




Rang & Dale's Pharmacology. 9th. 2021.

# Natural history of opportunistic infections (OIs) associated with HIV infection




The probability of developing specific OIs is closely related to CD4 count thresholds

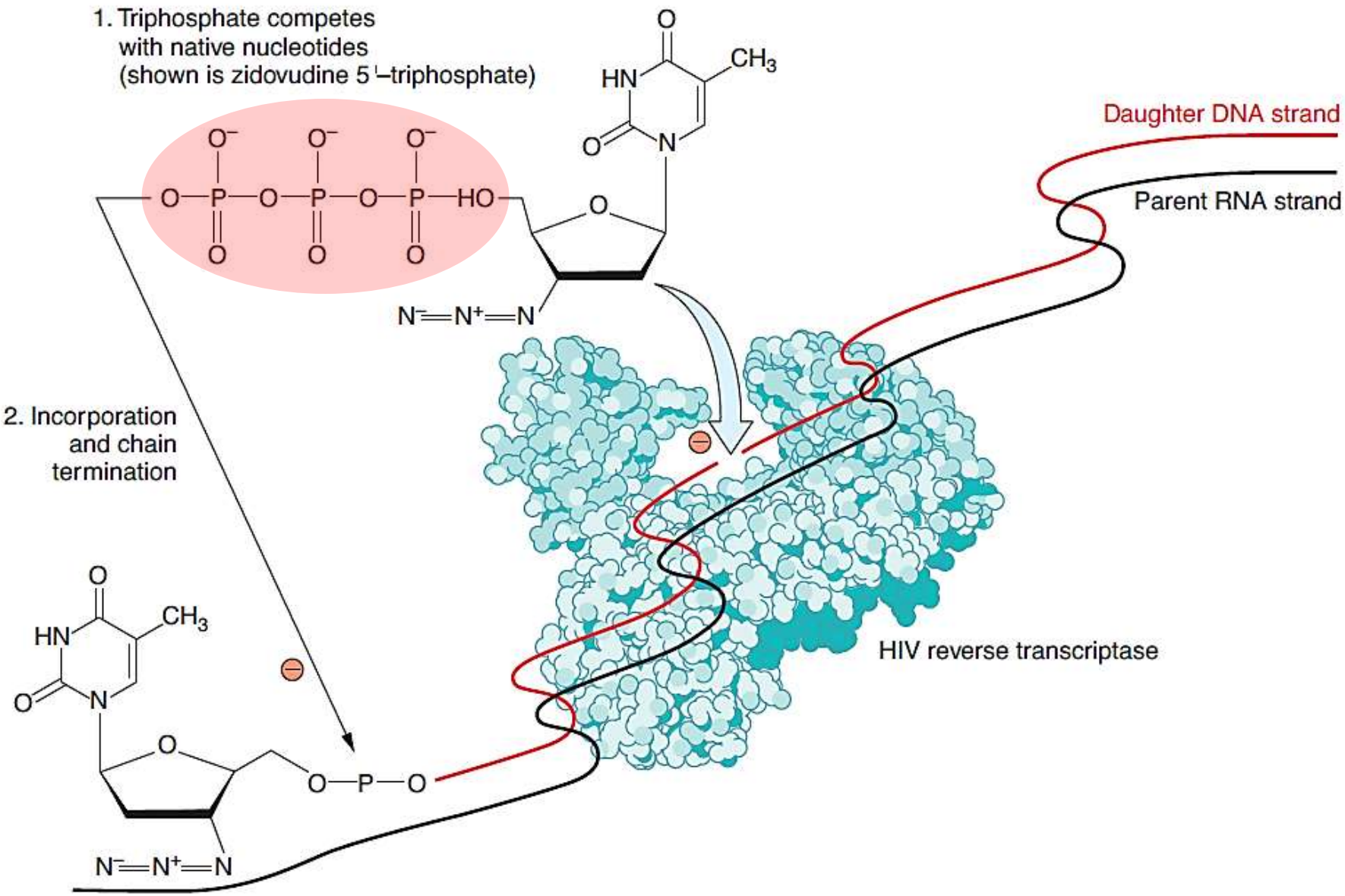
# Main classes of antiretroviral agents (ART)

1. **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs):**
   - **inhibition of viral genome replication**
2. **Non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs):**
   - **inhibition of viral genome replication**
3. **Protease inhibitors (PIs):**
   - **inhibition of viral maturation**
4. **Fusion inhibitors and CCR5 co-receptor antagonists (entry inhibitors):**
   - **inhibition of viral attachment & entry**
5. **HIV integrase strand transfer inhibitors (INSTIs):**
   - **Inhibition of viral genome replication**

# 1.
# Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

*Inhibition of viral genome replication*

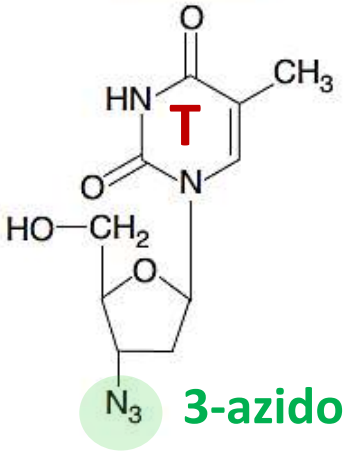
# Mechanism of NRTIs



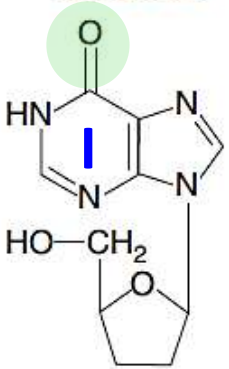

Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Structure of NRTIs

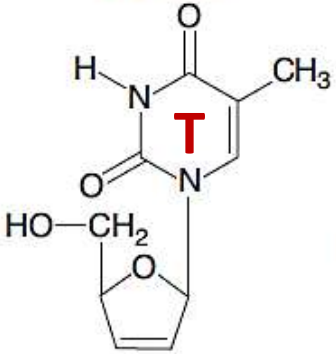
**AZT**
Zidovudine



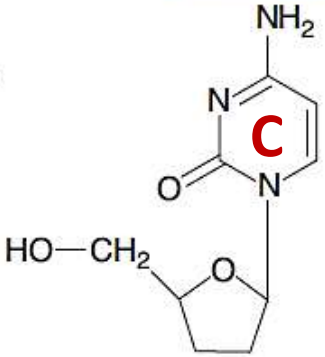

**ddI**
Didanosine



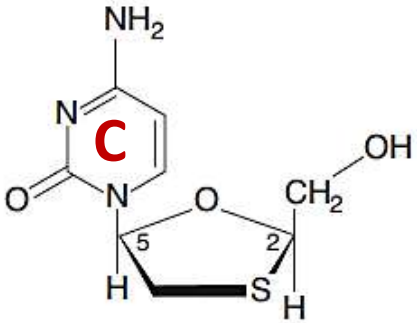

**d4T**
Stavudine



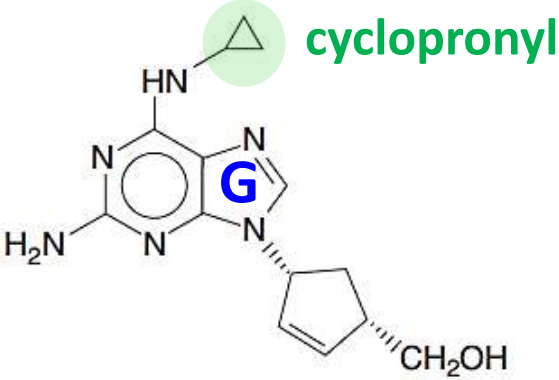

**ddC**
Zalcitabine



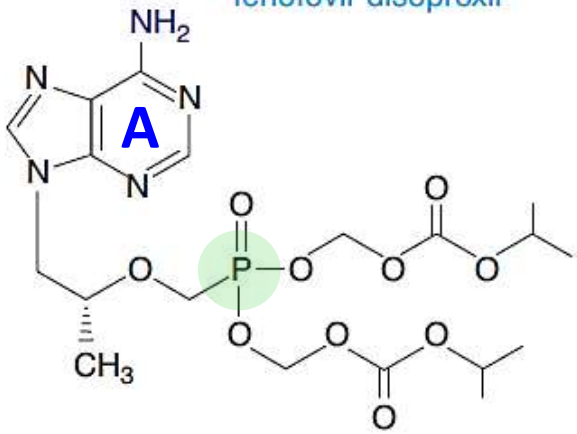

**3TC**
Lamivudine



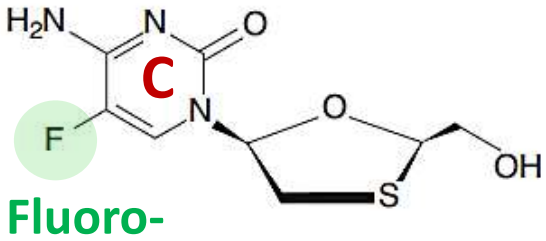

**ABC**
Abacavir




**TDF**
Tenofovir disoproxil

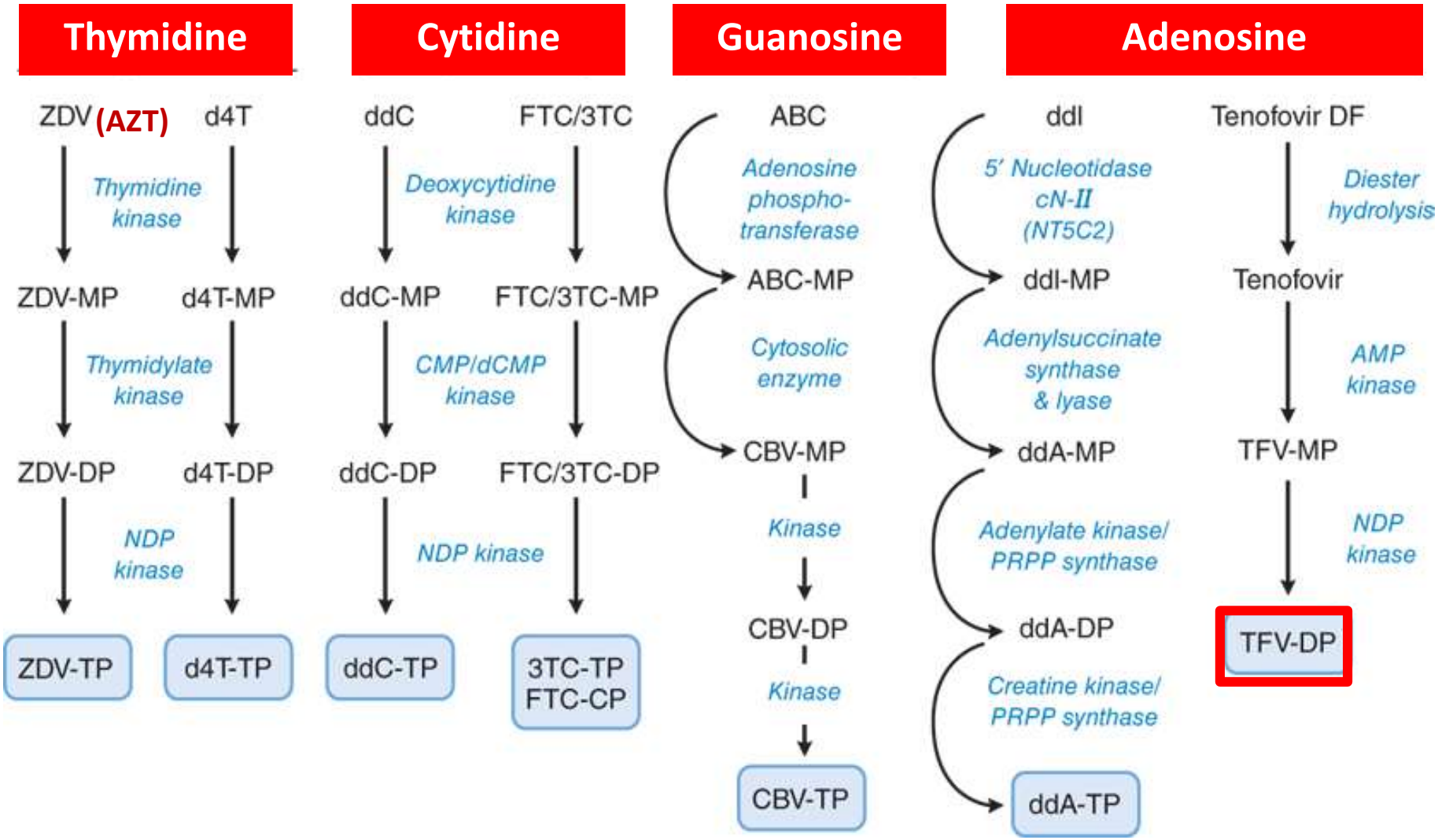



**FTC**
Emtricitabine




Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Intracellular activation of NRTIs






Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Abacavir (ABC)**<br>(Ziagen®) | 300 mg bid, 600 mg od | Rash<br>***Hypersensitivity reaction** (fatal)***<br>N/V<br>MI (posible) | • Avoid alcohol<br>• Testing HLA-B*5701 positive -> hypersensitivity<br>• Metab: alcohol dehydrogenase, glucoronyl-s-transferase<br>• Adjust dose in liver impairment |
| **Didanosine (ddI)**<br>(Videx®) | 400 mg od, 200 mg bid | ***Peripheral neuropathy, retinal changes***<br>***Pancreatitis,*** diarrhea, N/V, hyperuricemia<br>MI (possible) | • Avoid concurrent neuropathic drugs (eg, stavudine, zalcitabine, isoniazid), ribavirin, and alcohol<br>• Adjust dose in renal impairment |
| **Emtricitabine (FTC)**<br>(Emtriva®) | 200 mg od | Headache, asthenia<br>Diarrhea, N/V<br>***Skin hyperpigmentation (soles, palms)*** | • Adjust dose in renal impairment |

# Abacavir: คำแนะนำเพิ่มเติม

| ยา | คำแนะนำ |
|---|---|
| **ABC** | ควรพิจารณาส่งตรวจเลือดหา **HLA-B*5701** ก่อนเริ่มการรักษาถ้าทำได้<br>อย่างไรก็ตาม อุบัติการณ์ HLA-B*5701 ในคนเอเชียต่ำ |
| | แนะนำแก่ผู้ติดเชื้อเอชไอวีในการสังเกตอาการแสดงของ**ปฏิกิริยาแพ้ต่อ ABC** ในช่วง 6 สัปดาห์แรกที่เริ่มยา<br>• **อาการต่อไปนี้อย่างน้อย 2 ข้อ**: (1) ไข้ (2) ผื่น (3) อาการของระบบทางเดินอาหาร เช่น คลื่นไส้อาเจียน ท้องเสีย ปวดท้อง (4) อ่อนเพลีย ปวดเมื่อย (5) อาการของระบบทางเดิน หายใจ เช่น ไอ หายใจลำบาก คออักเสบ หรือมีผลการตรวจทางห้องปฏิบัติการที่ผิดปกติ ได้แก่ เอนไซม์ตับผิดปกติ creatine phosphokinase เพิ่มสูง lymphopenia หรือมีฝ้าในภาพถ่ายรังสีทรวงอก เป็นต้น<br>• **หากสงสัยว่าอาจจะแพ้ยาให้หยุดทันทีและไม่ควรให้ยาซ้ำ** เพราะอาจเกิดปฏิกิริยาแพ้อย่างรุนแรงและอันตรายถึงชีวิตได้ |
| | ห้ามใช้ ABC ในผู้ที่มีปัญหาตับแข็ง Child-Pugh Score of 7-12 |

# Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Lamivudine (3TC)**<br>(Epivir®) | 150 mg bid,<br>300 mg od | N/V<br>***Headache,***<br>dizziness, fatigue<br>***Pancreatitis (children)*** | • Adjust dose in renal impairment |
| **Stavudine (d4T)**<br>(Zerit®) | 30 mg bid | ***Peripheral neuropathy,***<br>neuromuscular weakness<br>***Lipodystrophy,***<br>hyperlipidemia<br>Pancreatitis | • Avoid concurrent neuropathic drugs (eg, ddI, zalcitabine, isoniazid) |
| **Tenofovir (TDF)**<br>(Viread®) | 300 mg od | N/V, diarrhea,<br>hepatotoxicity<br>Headache<br>***Renal toxicity,***<br>osteomalacia | • Adjust dose in renal impairment |

# Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Zalcitabine (ddC)**<br>(Hivid®) | 0.75 mg tid | Peripheral neuropathy, oral ulcerations<br>Pancreatitis, arthralgia<br>headache, N/V, rash | • Avoid concurrent neuropathic drugs (eg, ddI, stavudine, isoniazid) |
| **Zidovudine**<br>or azidothymidine<br>**(ZDV or AZT)**<br>(Retrovir®) | 200 mg tid, 300 mg bid | ***Macrocytic anemia, neutropenia,***<br>N/V, headache, insomnia, asthenia<br>Pancreatitis, lactic acidosis, hyperlipidemia, DM, ***myopathy*** | • First drug for HIV treatment<br>• Avoid concurrent myelosuppressive drugs (eg, ganciclovir, ribavirin)<br>• Adjust dose in renal impairment |

# PK of NRTIs

| PARAMETER | ZIDOVUDINE | LAMIVUDINE | STAVUDINE[b] | DIDANOSINE[c] |
|---|---|---|---|---|
| Oral bioavailability, % | 64 | 86–87 | 86 | 42 |
| Effect of meals on AUC | ↓ 24% (high fat) | ↔ | ↔ | ↓ 55% (acidity) |
| Plasma $t_{1/2}$, h | 1.0 | 5–7 | 1.1–1.4 | 1.5 |
| Intracellular $t_{1/2}$ of triphosphate, h | 3–4 | 12–18 | 3.5 | 25–40 |
| Plasma protein binding, % | 20–38 | <35 | <5 | <5 |
| Metabolism, % | 60–80 (glucuronidation) | <36 | ND | 50 (purine metabolism) |
| Renal excretion of parent drug, % | 14 | 71 | 39 | 18–36 |



Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# PK of NRTIs

| PARAMETER | ABACAVIR | TENOFOVIR[d] | EMTRICITABINE |
|---|---|---|---|
| Oral bioavailability, % | 83 | 25 | 93 |
| Effect of meals on AUC | ↔ | ↑ 40% (high fat) | ↔ |
| Plasma $t_{1/2}$, h | 0.8–1.5 | 14–17 | 10 |
| Intracellular $t_{1/2}$ of triphosphate, h | 21 | 60–100 | 39 |
| Plasma protein binding, % | 50 | <8 | <4 |
| Metabolism, % | >80 (dehydrogenation; glucuronidation) | ND | 13 |
| Renal excretion of parent drug, % | <5 | 70–80 | 86 |

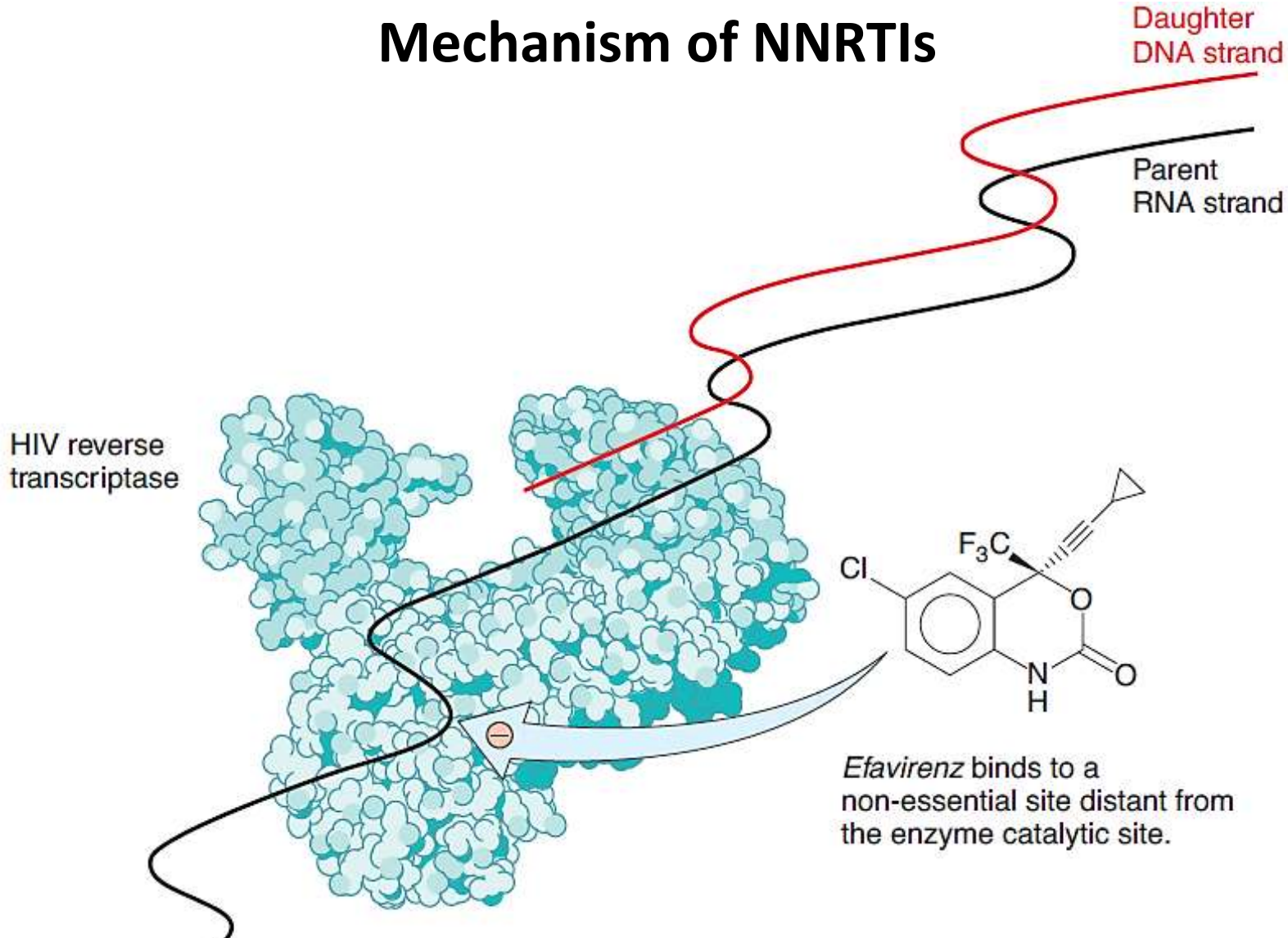


Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# 2.
# Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

*Inhibition of viral genome replication*

# Mechanism of NNRTIs

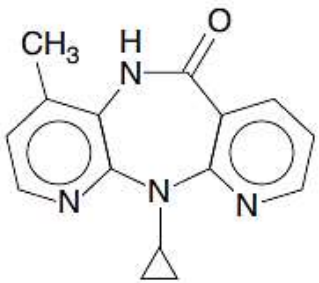



**Bind near catalytic side of reverse transcriptase (RT) -> prevent enzyme from joining deoxyribonucleotides with the primer-strand template**

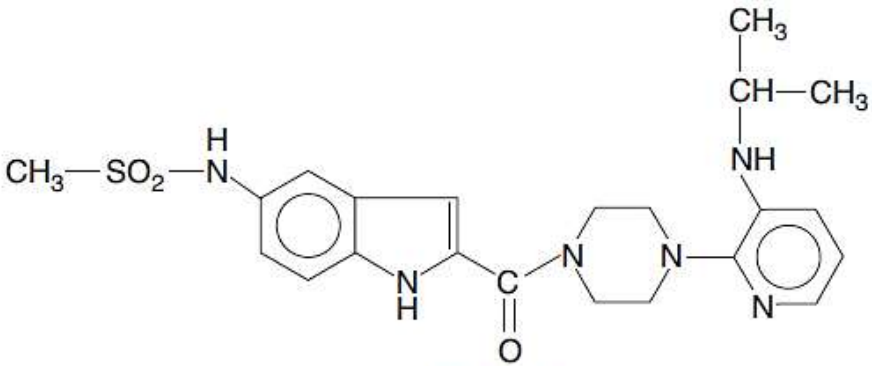


Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

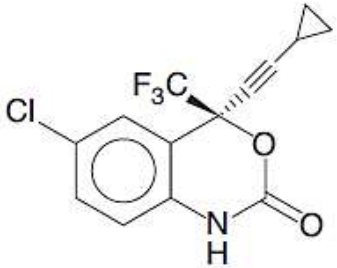
# Structure of NNRTIs



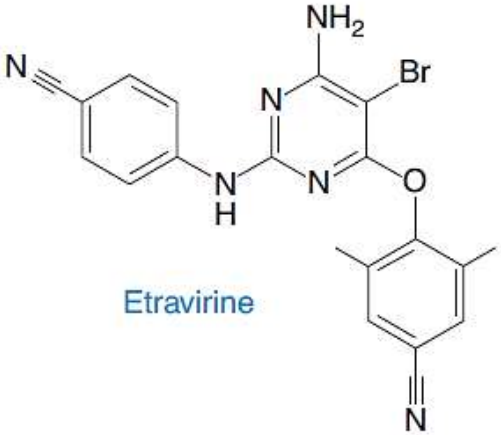

Nevirapine




Delavirdine




Efavirenz




Etravirine

**Structures of the NNRTIs are significantly different from those of the anti-HIV nucleoside and nucleotide analogues.**



Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Delavirdine (DLV)**<br>(Rescriptor®) | 400 mg tid | ***Rash***<br>***↑ liver enzymes***<br>Headache, N/V, diarrhea | • **Concurrent use of drugs metabolized by CYP3A4 is contraindicated for all NNRTIs** |
| **Efavirenz (EFV)**<br>(Sustiva®) | 600 mg od | ****CNS effects (psychiatric symp, depression, suicidal ideation)***<br>Rash<br>↑ liver enzymes<br>Headache, N/V | • Take on an empty stomach (decrease S/E)<br>• Bedtime dosing recommended to minimize CNS S/E<br>• Metab: 2B6, 3A4 |

# Non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Etravirine (ETR)**<br>(Intelence®) | 200 mg bid | ***Rash***<br>***N/V,*** diarrhea | • Take after a meal (not empty stomach)<br>• Do not administer with other NNRTIs<br>• Metab: 3A4, 2C9, 2C19 |
| **Nevirapine (NVP)**<br>(Viramune®) | 200 mg bid | ***Rash***<br>***Serious hepatotoxicity, hepatitis***<br>Headache, N/V | • Adjust dose in hepatic insufficiency<br>• Metab: 2B6, 3A4 |
| **Rilpivirine (RPV)**<br>(Edurant®) | 25 mg od | Insomnia, ***depression***<br>Rash<br>↑ liver enzymes | • Metab: 3A4<br>• Avoid concurrent proton pump inhibitors |

# PK of NNRTIs

| PARAMETER | NEVIRAPINE[b] | EFAVIRENZ[b] | ETRAVIRINE | RILPIVIRINE |
|---|---|---|---|---|
| Oral bioavailability, % | 90–93 | 50 | NR | NR |
| Effect of meals on AUC | ↔ | ↑ 17%–28% | ↑ 33%–102% | ↑ 40%–50% |
| Plasma $t_{1/2}$, h | 25–30 | 40–55 | 41 | 50 |
| Plasma protein binding, % | 60 | 99 | 99.9 | 99.7 |
| Metabolism by CYPs and UGT | 3A4 > 2B6 | 2B6 > 3A4 | 3A4, 2C9, 2C19, UGT | 3A4, 3A5 |
| Renal excretion of parent drug, % | <3 | <3 | 1% | 6% |
| Autoinduction of metabolism | Yes | Yes | NR | No |
| Inhibition of CYP3A | No | Yes | No | No |

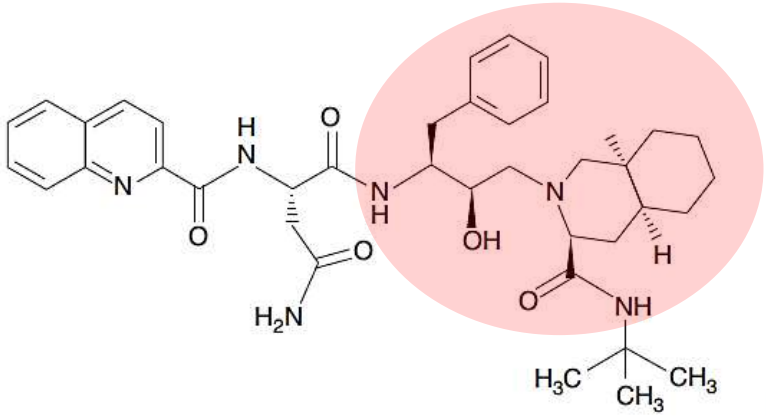


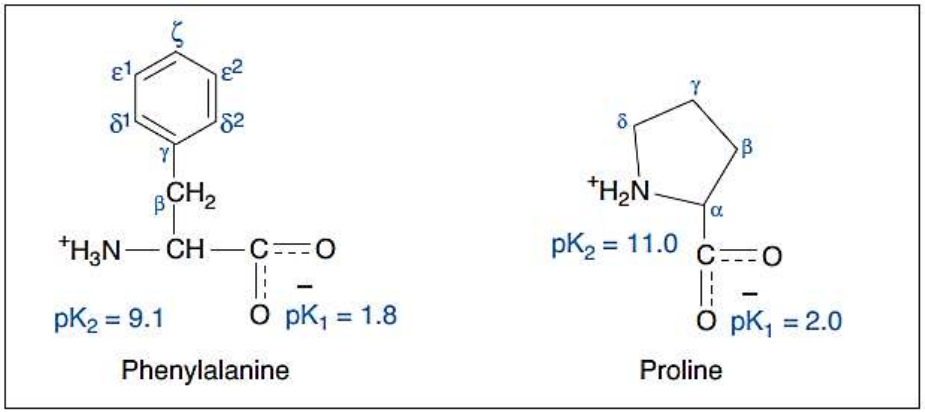
Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

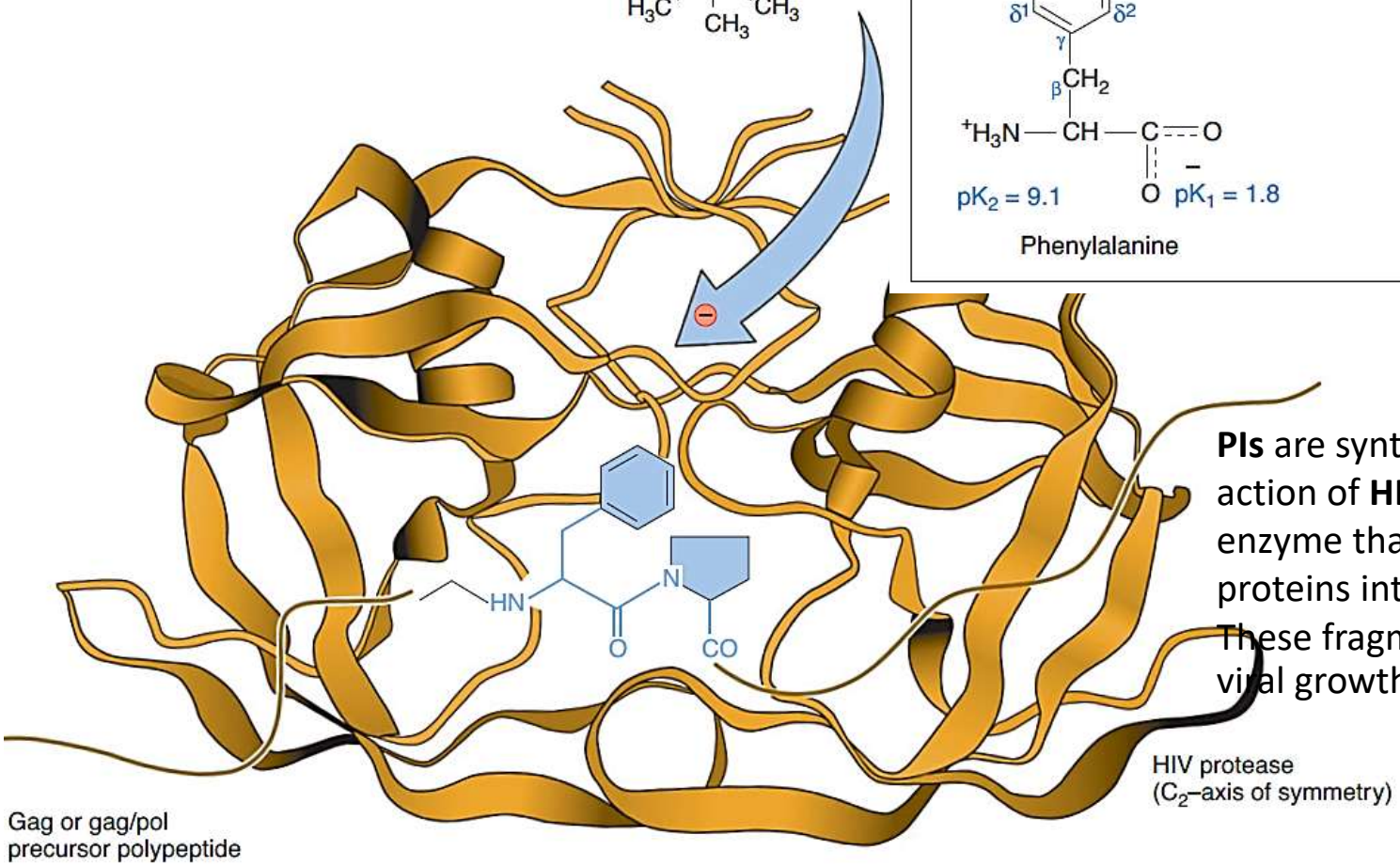
# 3.
# Protease inhibitors
# (PIs, -navir)

*Inhibition of viral maturation*

# Mechanism of PIs



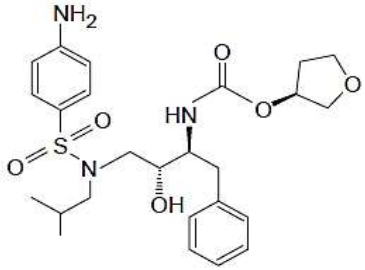




**PIs** are synthetic drugs that **inhibit** action of **HIV-1 protease**, an enzyme that cleaves 2 precursor proteins into smaller fragments. These fragments are needed for viral growth and replication

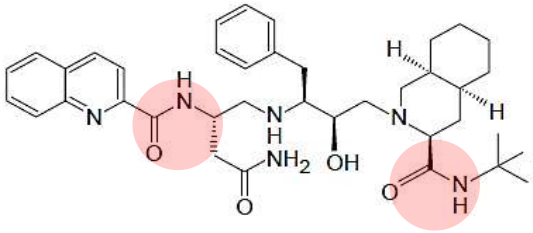


Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Structure of PIs

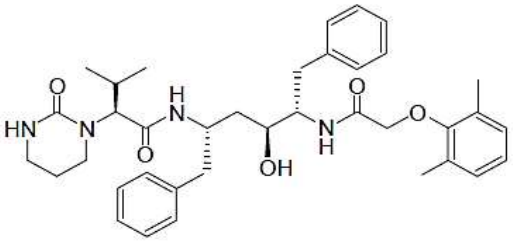


Amprenavir

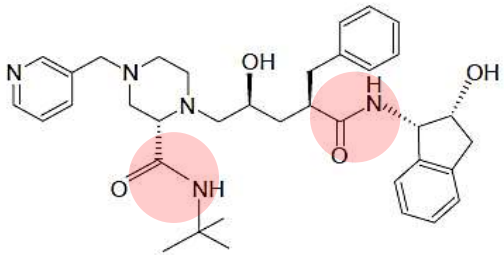


Saquinavir

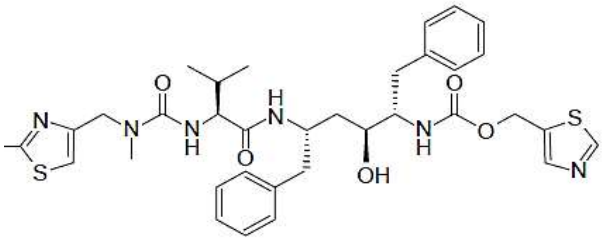
## Peptidomimetics



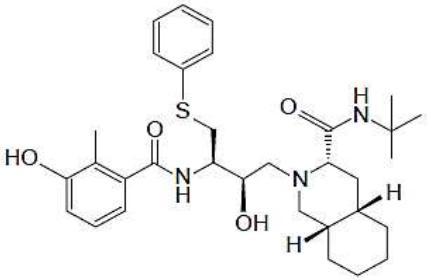
Lopinavir



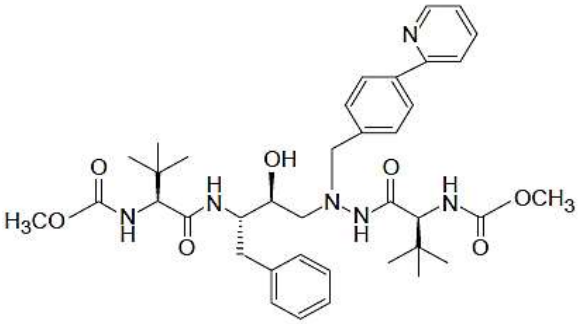
Indinavir



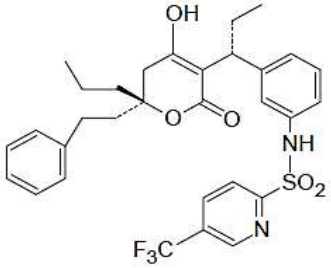
Ritonavir



Nelfinavir



Atazanavir



Tipranavir

Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Protease inhibitors (PIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Atazanavir (ATV)**<br>(Reyataz®) | 400 mg od with ritonavir<br>100 mg od | N/V, diarrhea, abdominal pain<br>Headache, rash<br>Peripheral neuropathy<br>***Indirect hyperbilirubinemia***<br>Prolonged PR or QTc interval | • Adjust dose in hepatic insufficiency<br>• Take with food<br>• Separate dosing from cimetidine and other acid-reducing agents by 12 h<br>• Metab: CYP3A4 |
| **Darunavir (DRV)**<br>(Prezista®) | 600 mg bid with ritonavir<br>100 mg bid | N/V, diarrhea<br>Headache, rash<br>Hyperlipidemia, ***hepatitis***,<br>↑ liver enzymes, ↑ serum amylase | • Take with food<br>• Avoid in patients with sulfa allergy<br>• Metab: CYP3A4 |
| **Nelfinavir (NFV)**<br>(Viracept®) | 750 mg tid | N/V, ***diarrhea,*** flatulence | • Take with food |

# Protease inhibitors (PIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Indinavir (IDV)**<br>(Crixivan®) | 800 mg bid with ritonavir 100mg bid | ***Nephrolithiasis***<br>Indirect hyperbilirubinemia<br>N/V, headache, asthenia, blurred vision | • Adjust dose in hepatic insufficiency<br>• Best on an empty stomach<br>• Drink at least 48 oz liquid daily |
| **Lopinavir/ ritonavir (LPV/r)**<br>(Kaletra®) | 400 mg/100 mg bid | Diarrhea, abdominal pain, N/V, ***GI intolerance***<br>***Hypertriglyceridemia***<br>Headache<br>↑ liver enzymes | • Adjust dose in hepatic insufficiency<br>• Take with food<br>• Metab: CYP3A4 |
| **Fosampre-navir (FPV)**<br>(Lexiva®) | 1400 mg bid with ritonavir 100 mg bid | Diarrhea, N/V<br>Hypertriglyceridemia<br>***Rash,*** headache, peripheral paresthesias<br>↑ liver enzymes | • Adjust dose in hepatic insufficiency<br>• Avoid concurrent high-fat meals<br>• Fosamprenavir is a prodrug form of amprenavir with greater oral bioavailability |

# Protease inhibitors (PIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Ritonavir (RTV)**<br>(Norvir®) | 600 mg bid | N/V, ***GI intolerance,*** diarrhea<br>Paresthesias<br>Hepatitis | • Take with food |
| **Saquinavir (SQV)**<br>(Invirase®) | 1000 mg bid with ritonavir 100 mg bid | N/V, diarrhea, abdominal pain, dyspepsia<br>***QT prolongation***<br>Rhinitis<br>Rash | • Take within 2 h of a full meal<br>• Adjust dose in hepatic insufficiency<br>• Use sunscreen owing to an increase in photosensitivity |
| **Tipranavir (TPV)**<br>(Aptivus®) | 500 mg bid with ritonavir 200 mg bid | N/V, diarrhea, abdominal pain<br>Rash<br>***↑ liver enzymes,***<br>hypercholesterolemia,<br>hypertriglyceridemia | • Avoid use in hepatic insufficiency<br>• Take with food<br>• Avoid in patients with sulfa allergy<br>• Do not administer to patients at risk for bleeding |

# PK of PIs

| PARAMETER | SAQUINAVIR[b] | INDINAVIR | RITONAVIR |
|---|---|---|---|
| Bioavailability (oral), % | 13 | 60-65 | >60 |
| Effect of meals on AUC | ↑ 570% (high fat) | ↓ 77% (high fat) | ↑ 13% (capsule) |
| Plasma $f_{1/2}$, h | 1-2 | 1.8 | 3-5 |
| Plasma protein binding, % | 98 | 60 | 98-99 |
| Metabolism by CYPs | 3A4 | 3A4 | 3A4 > 2D6 |
| Autoinduction of metabolism | No | No | Yes |
| Renal excretion of parent drug, % | <3 | 9-12 | 3.5 |
| Inhibition of CYP3A4 | + | ++ | +++ |



Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# PK of PIs

| PARAMETER | NELFINAVIR | FOSAMPRENAVIR | LOPINAVIR[c] |
|---|---|---|---|
| Bioavailability (oral), % | 20-80 (formulation and food dependent) | ND | ND |
| Effect of meals on AUC | ↑ 100%-200% | ↔ | ↑ 27% (moderate fat) |
| Plasma $f_{1/2}$, h | 3.5-5 | 7.7 | 5-6 |
| Plasma protein binding, % | >98 | 90 | 98-99 |
| Metabolism by CYPs | 2C19>3A4 | 3A4 | 3A4 |
| Autoinduction of metabolism | Yes | No | Yes |
| Renal excretion of parent drug, % | 1-2 | 1 | <3 |
| Inhibition of CYP3A4 | ++ | ++ | +++ |



Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# PK of PIs

| PARAMETER | ATAZANAVIR | TIPRANAVIR | DARUNAVIR |
|---|---|---|---|
| Bioavailability (oral), % | ND | ND | 82 |
| Effect of meals on AUC | ↑ 70% (light meal) | ↔ | ↑ 30% |
| Plasma $f_{1/2}$, h | 6.5-7.9 | 4.8-6.0 | 15 |
| Plasma protein binding, % | 86 | 99.9 | 95 |
| Metabolism by CYPs | 3A4 | 3A4 | 3A4 |
| Autoinduction of metabolism | No | Yes | ND |
| Renal excretion of parent drug, % | 7 | 0.5 | 8 |
| Inhibition of CYP3A4 | ++ | +++ | +++ |



Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

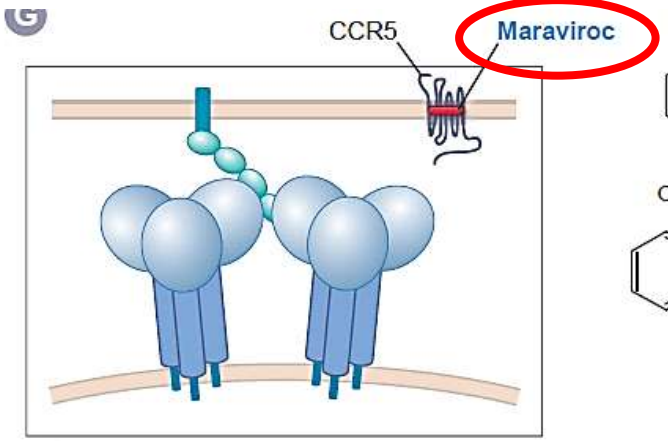
# 4.
# Fusion inhibitors & CCR5 co-receptor antagonists (entry inhibitors)

*Inhibition of viral attachment & entry*

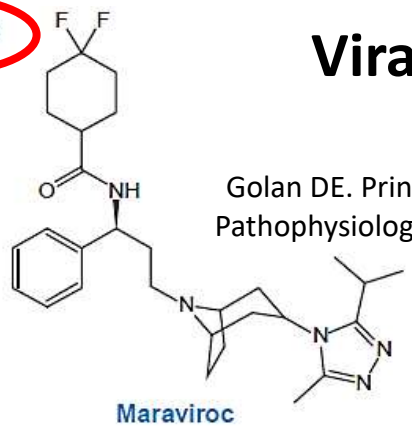
# Viral attachment & entry

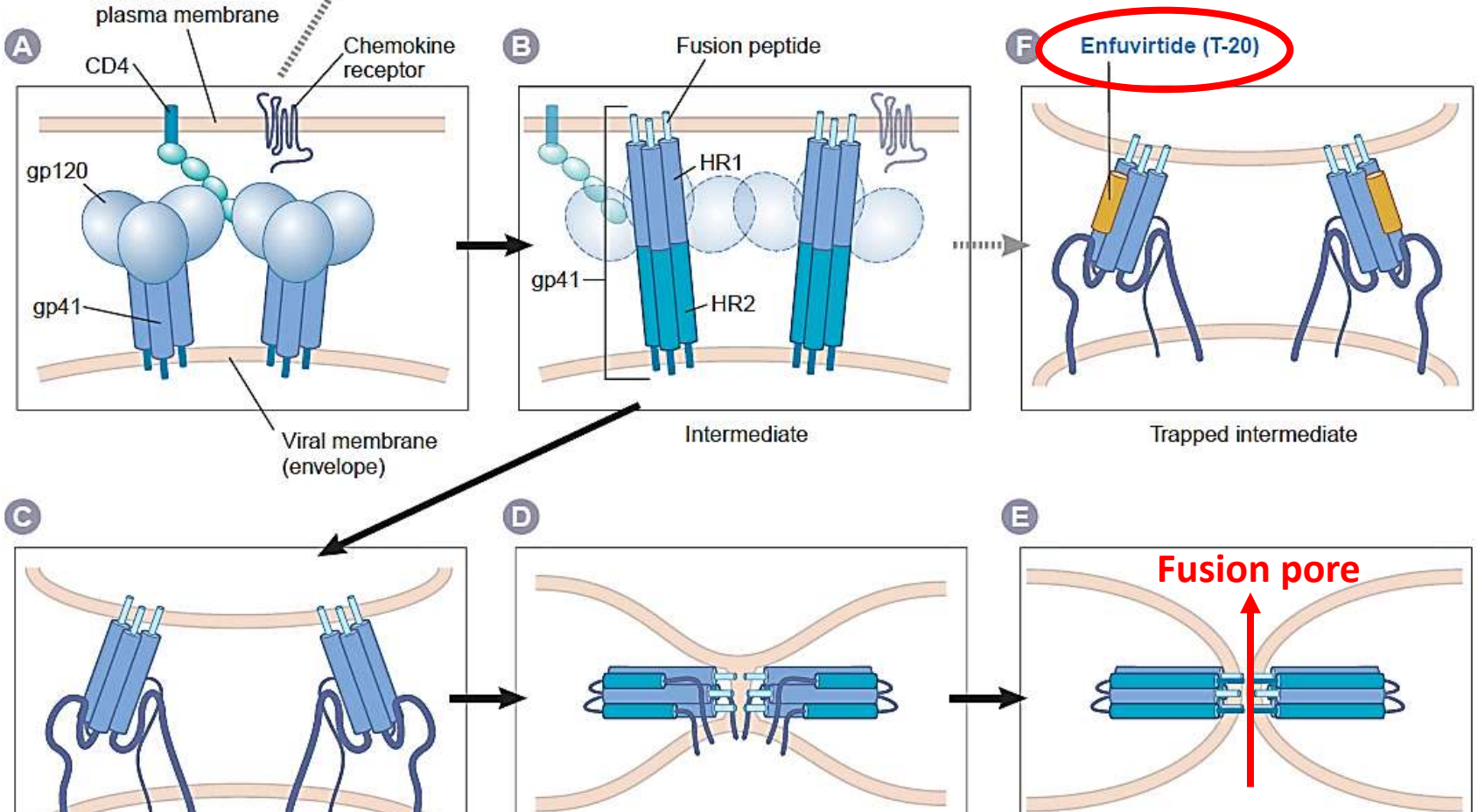
Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th, 2016

**Fusion peptide**
**HR: heptad-repeat region**




CCR5 blocked by maraviroc



# Maraviroc (Selzentry®)

- **Group:** Inhibitors of viral attachment and entry
- **Mechanism:** Block chemokine receptor (CCR5)
- **Clinical uses:** HIV
- **ADR:**
  - Hepatitis
  - Myocardial infarction, orthostatic hypotension
  - Rash, dizziness, risk of infection (URI), fever, cough
- **Consideration:**
  - Maraviroc blocks infection of HIV strains that use CCR5 for attachment and entry, but it is not active against HIV strains that use CXCR4 receptor
  - Used in combination with other anti-HIV drugs in patients who have detectable viral loads or who have multidrug-resistant virus
  - Dose: 150 mg bid, Metab: CYP3A4

# Enfuvirtide (Fuzeon®)

- **Group:** Inhibitors of viral attachment and entry
- **Mechanism:** Inhibit gp41-mediated fusion of HIV envelope with host plasma membrane
- **Clinical uses:** HIV
- **ADR:**
  - Renal insufficiency
  - Thrombocytopenia, neutropenia, eosinophilia
  - Peripheral neuropathy, conjunctivitis
- **Contraindication:**
- **Consideration:**
  - Enfuvirtide is a peptide -> administer parenteral, twice-daily
  - Used in combination with other anti-HIV drugs in patients whose HIV has not been controlled on other anti-HIV drugs

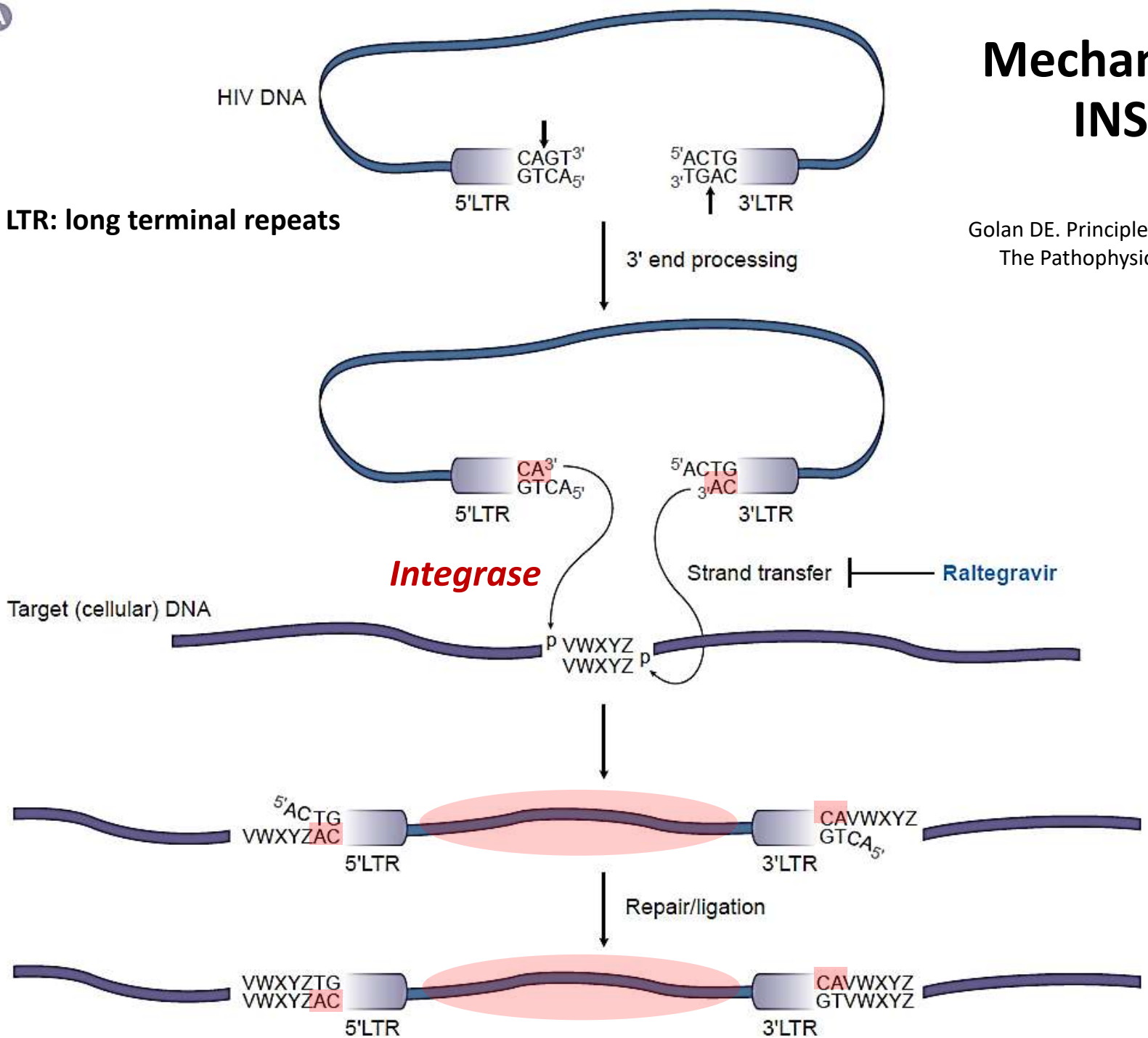
# 5.
# HIV integrase strand transfer inhibitors (INSTIs, -gravir)

*Inhibition of viral genome replication*

# Mechanism of INSTIs

**LTR: long terminal repeats**

Golan DE. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 4th, 2016



# HIV integrase strand transfer inhibitors (INSTIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Raltegravir (RAL)**<br>(Isentress®) | 400 mg bid | Suicidal risk, insomnia, headache, dizziness<br>Diarrhea, N/V<br>Muscle aches, ↑ liver enzymes, ↑ ***creatine kinase***, rhabdomyolysis<br>Renal failure<br>Hypersensitivity reaction | • Metab: UGT1A1 glucoronidation |
| **Dolutegravir (DTG)**<br>(Tivicay®) | 50 mg od | Insomnia, headache<br>Hypersensitivity reaction<br>↑ liver enzymes | • Metab: UGT1A1 glucoronidation |

UGT1A1 : UDP glucuronosyltransferase family 1 member A1

# HIV integrase strand transfer inhibitors (INSTIs)

| Agent | Adult Dosage | Adverse Effects | Consideration |
|---|---|---|---|
| **Elvitegravir (EVG)**<br>(Stribild®) | 150 mg od | **N/V, diarrhrea**<br>Renal impairment<br>Decreased bone mass density | • Available in combined formulation with cobicistat, tenofovir, and emtricitabine<br>• Metab:<br>EVG :CYP3A4, UGT1A1<br>Cobi: CYP3A4, 2D6 |
| **Bictegravir (BIC)**<br>(Biktarvy®) | 50 mg od | Diarrhea, nausea<br>Headache | • Available in combined formulation with emtricitabine and tenofovir alafenamide<br>• Metab: UGT1A1 glucoronidation |

# PK of INSTIs

| PARAMETER | RALTEGRAVIR | ELVITEGRAVIR[b] | DOLUTEGRAVIR | BICTEGRAVIR |
|---|---|---|---|---|
| Oral bioavailability, % | NR | NR | NR | NR |
| Effect of meals on AUC | ↔ | ↑ 34%–87% | ↑ 33%–66% | ↑ 24% |
| Plasma $t_{1/2}$, h | 9 | 12.9 | 14 | 17.3 |
| Plasma protein binding, % | 83 | 99 | 98.9 | >99 |
| Metabolism by CYPs and UGT | UGT1A1 | CYP3A4 (major)<br>UGT1A1/3 (minor) | UGT1A1 > CYP3A4 | CYP3A4, UGT1A1 |
| Renal excretion of parent drug, % | 9 | 6.7 | <1% | NR |
| Inhibition of CYP3A | No | Yes | No | No |



Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th, 2023

# Current Treatment of HIV/AIDS

- **The use of retroviral therapy in AIDS has emerged based on the following principles:**
  - **Monitor plasma viral load and CD4+ cell count**
  - **Start treatment before immunodeficiency becomes evident**
  - **Aim to reduce plasma viral concentration as much as possible for as long as possible**
  - **Use combinations of at least 3 drugs "HAART protocol"**
  - **Change to a new regimen if plasma viral concentration increases**

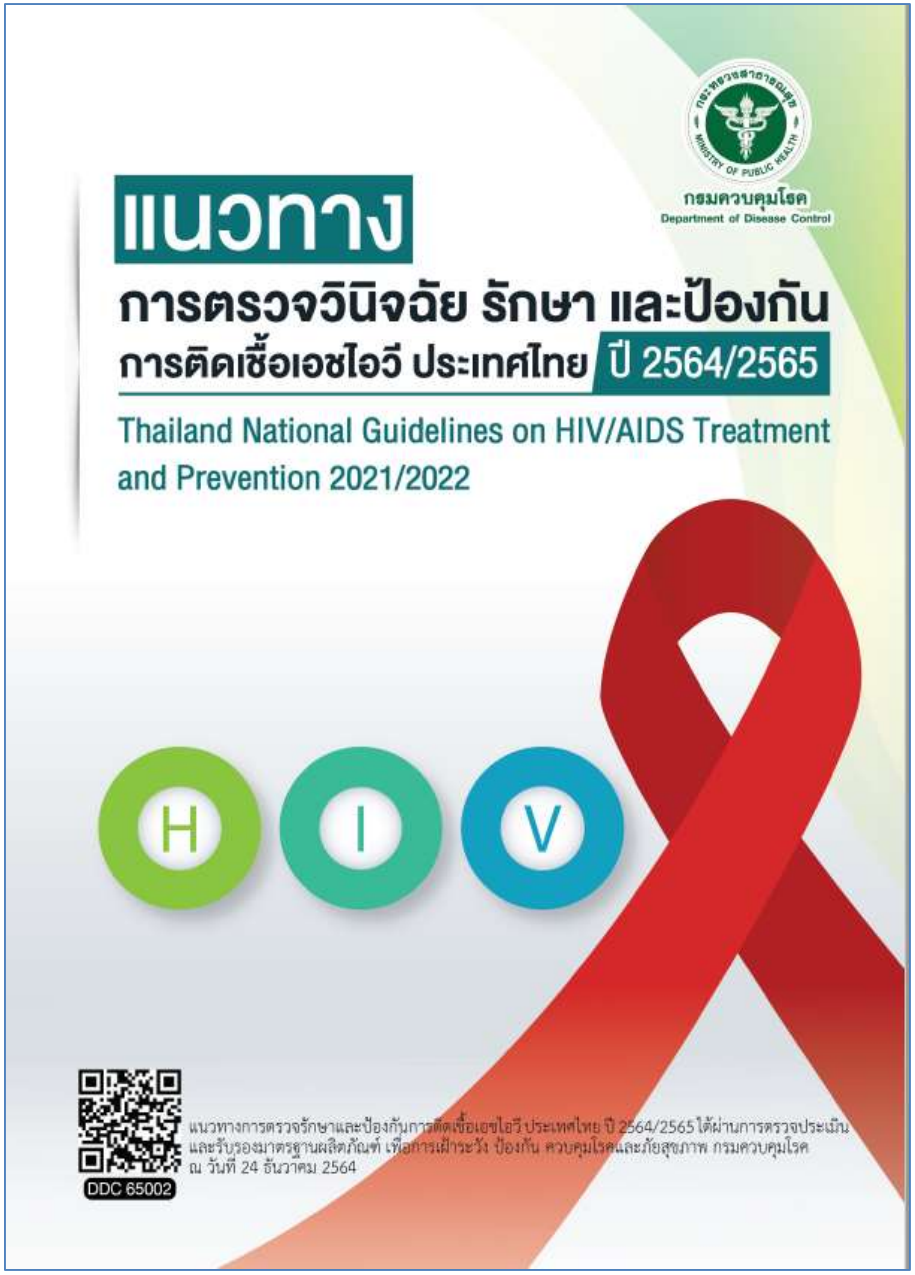
เกณฑ์การเริ่มยาต้านเอชไอวีในประเทศไทย

*** ให้ ART ในผู้ติดเชื้อทุกรายในทุกจำนวน CD4 ที่มีความพร้อมของการกินยาระยะยาว **

(ประโยชน์และผลข้างเคียงของยา, Adherence, ยินดีที่จะเริ่ม+มุ่งมั่นตั้งใจรับ ART สม่ำเสมอตลอดชีวิต)

# Combination therapy for HIV: HAART protocol

- Combination therapy for HIV: "Highly active antiretroviral therapy (HAART)"
- **Pros:**
  - HIV replication is inhibited
  - Reduce plasma HIV RNA to undetectable levels
  - Prolonged survival rate
- **Cons:**
  - Regimen is complex, many unwanted effects
  - Compliance is difficult and lifelong treatment is necessary
  - Drug interactions, inter-individual variations in absorption
  - Metabolic and cardiovascular complications
  - Some drugs penetrate poorly into brain -> local proliferation of virus
  - Cross-resistance could be a problem in the future
  - Children, pregnant or breastfeeding women -> Specific guidelines




**สำนักโรคเอดส์ วัณโรค และโรคติดต่อทางเพศสัมพันธ์ กรมควบคุมโรค กระทรวงสาธารณสุข**

# สูตรยาต้านเอชไอวีที่แนะนำเป็นสูตรแรกและสูตรทางเลือกในประเทศไทย

- ART ที่แนะนำให้ใช้เป็นสูตรแรกในไทยคือ 2NRTIs + DTG โดยแนะนำให้เป็นแบบรวมเม็ด เนื่องจากควบคุมไวรัสได้ดี, ผลข้างเคียงน้อย, และใช้วันละครั้ง

| NRTIs backbone | | ยาตัวที่ 3 |
|---|---|---|
| แนะนำ | + | แนะนำ |
| (TDF หรือ TAF) ร่วมกับ (3TC หรือ FTC) | | DTG[1] |
| หรือทางเลือก | | หรือทางเลือก |
| ABC + 3TC<br>AZT + 3TC | | EFV หรือ RPV |

- สูตรทางเลือก: NRTIs + NNRTIs : (TDF หรือ TAF) ร่วมกับ (3TC หรือ FTC) + EFV หรือ RPV
- กรณีที่ใช้ TDF หรือ TAF ไม่ได้: แนะนำให้ใช้ NRTIs backbone เป็น ABC/3TC หรือ AZT+3TC
- กรณีใช้ DTG ไม่ได้: อาจใช้กลุ่ม integrase inhibitor (EVG, RAL, BIC) หรือ protease inhibitors (ATV/r, DRV/r, LPV/r)

# Pharmacokinetic enhancers (CYP3A Inhibitors)

- **PK enhancers** is used to boost the effectiveness of another drug
- CYP3A4 is responsible for metabolizing most PIs
- PK enhancers in HIV regimens (CYP3A Inhibitors): Ritonavir, cobicistat
- PK enhancers: Co-administration improves PK profiles of concomitant PIs -> enhance the effectiveness of PI treatment
  - reduce pill burden & simplify dosing regimens
  - improve therapy adherence
- However, side effects of ritonavir is GI problems, lipid disturbances

- Example:
  - Cobicistat-boosted atazanavir (ATZ/c)
  - Cobicistat-boosted darunavir (DRV/c)
  - Ritonavir-boosted atazanavir (ATZ/r)
  - Ritonavir-boosted darunavir (DRV/r)

# PK parameters of ART given with & without boosting agents

| Drug or combination | $N$ | Dose (mg) | $C_{max}$ (mg/L) | $C_{min}$ (mg/L) | AUC (mg·h/L) | $t_{½}$ (h) |
|---|---|---|---|---|---|---|
| Protease inhibitors | | | | | | |
| Atazanavir[a] | 13 | 400 QD | 3.15 ± 2.23 | 0.27 ± 0.30[b] | 22.3 ± 20.2 | 6.5 ± 2.6 |
| Atazanavir/RTV[a] | 10 | 300/100 QD | 5.23 ± 3.03 | 0.86 ± 0.84 | 53.8 ± 35.3 | 8.6 ± 2.3 |
| Atazanavir/COBI[c] | 34 | 300/150 QD | 4.88 (24.9) | 1.33 (42.7)[d] | 55.9 (28.2)[e] | 16.7 (11.7– 20.4) |
| Darunavir[a] | 4 | 400 QD | 2.73 ± 0.65 | NA | 4.75 ± 1.65[g] | 29.4 ± 45.3 |
| Darunavir/RTV[a] | 4 | 400 QD/100 BID | 5.13 ± 0.91 | NA | 50.76 ± 15.6[g] | 13.5 ± 1.83 |
| Darunavir/COBI[a] | 38 | 800/150 SD | 6.97 ± 1.201 | NA | 79.8 ± 26.9[g, h] | 5.5 ± 1.6[h] |
| Darunavir/COBI[c] | 33 | 800/150 QD | 7.74 (21.8) | 1.33 (66.8)[d] | 81.1 (31)[i] | NA |
| Darunavir/COBI[c] | 24 | 600/150 BID | 9.04 (19) | 3.96 (30)[d] | 73.4 (19)[j] | NA |
| Fosamprenavir[k] | 22 | 1,400 BID | 4.82 (4.06–5.72) | 0.35 (0.27–0.46)[d] | 33.0 (27.6–39.2)[i] | NA |
| Fosamprenavir/RTV[k] | 22 | 1,400/200 QD | 7.24 (6.32–8.28) | 1.45 (1.16–1.81)[d] | 69.4 (59.7–80.8)[i] | NA |
| Fosamprenavir/RTV[k] | 36 | 1,400/100 QD | 7.93 (7.25–8.68) | 0.86 (0.74–1.01)[d] | 66.4 (61.1–72.1)[i] | NA |
| Fosamprenavir/RTV[k] | 24 | 700/100 BID | 6.08 (5.38–6.86) | 2.12 (1.77–2.54)[d] | 79.2 (69.0–90.6)[i] | NA |
| Integrase inhibitor | | | | | | |
| Elvitegravir/COBI[c] | 40 | 150/150 QD | 2.66 (27.6 %) | 0.49 (52.9 %)[d] | 27.0 (29.4 %)[e] | 9.15 (7.70–12.4)[f] |

Larson KB, et al. Clin Pharmacokinet 2014;53:865-72

# Glossary: Anti-HIVs

| Entry inhibitors | NRTIs | NNRTIs | INSTIs (-gravir) | PIs (-navir) |
|---|---|---|---|---|
| **CCR5 antagonist** | ABC Abacavir | ETR Etravirine | DTG Dolutegravir | ATV Atazanavir |
| MVC Maraviroc | AZT, ZDV Zidovudine | EFV Efavirenz | EVG Elvitegravir | DRV Darunavir |
| | ddI Didanosine | NVP Nevirapine | RAL Raltegravir | IDV Indinavir |
| **Fusion inhibitor** | ddC Zalcitabine | RPV Rilpivirine | BIC Bictegravir | LPV Lopinavir |
| ENF Enfuvirtide | FTC Emtricitabine | DLV Delavirdine | | NFV Nelfinavir |
| | 3TC Lamivudine | | | RTV Ritonavir |
| | d4T Stavudine | | | SQV Saquinavir |
| | TDF Tenofovir disoproxil fumarate | | | FPV Fosamprenavir |
| | | | | TPV Tipranavir |
| | TAF Tenofovir alafenamide | | | /r Ritonavir boosted |
| | | | | COBI Cobicistat |

# บัญชียาหลักแห่งชาติ 2565

## 5.3 Antiviral drugs

### 5.3.1 Non-antiretrovirals

Aciclovir ชนิด topical (Aciclovir cream) ไม่จัดเป็นยาในบัญชียาหลักแห่งชาติ เนื่องจากมีประสิทธิผลต่ำ และไม่แนะนำให้ใช้

1. Aciclovir (Acyclovir) tab, oral susp, oral susp (hosp) ก

**หมายเหตุ**

ไม่แนะนำให้ใช้ในเด็กที่เป็นโรคอีสุกอีใส (Chicken pox) ชนิดไม่รุนแรง

2. Aciclovir sodium (Acyclovir sodium) sterile pwdr, sterile sol ค

**เงื่อนไข**

1. ใช้สำหรับการติดเชื้อไวรัส varicella - zoster และ herpes simplex ในผู้ป่วยที่มีภูมิคุ้มกันบกพร่องและในทารกแรกเกิด
2. ใช้สำหรับการติดเชื้อไวรัส varicella-zoster และ herpes simplex ที่มีการแพร่กระจาย หรือเป็นการติดเชื้อของอวัยวะภายใน หรือในผู้ป่วยที่ใช้ยารับประทานไม่ได้
3. ใช้กับทารกแรกเกิดที่มารดาป่วยเป็นโรคไข้อีสุกอีใสในช่วง 5 วันก่อนคลอดและในช่วง 2 วันหลังคลอด เพื่อป้องกันโรคอีสุกอีใสในทารกแรกเกิด (neonatal varicella)
4. ใช้ในกรณีพิเศษตามคำแนะนำของแพทย์ผู้เชี่ยวชาญด้านโรคติดเชื้อ

3. Oseltamivir phosphate cap, dry syr ค

**เงื่อนไข**

1. ใช้สำหรับการรักษาโรคไข้หวัดใหญ่ ในผู้ที่มีความเสี่ยงต่อการดำเนินโรครุนแรง หรือแพร่กระจายเชื้อให้ผู้ป่วยที่มีความเสี่ยงต่อการดำเนินโรครุนแรง
2. ใช้สำหรับรักษาโรคไข้หวัดใหญ่ที่มีอาการมาไม่เกิน 48 ชั่วโมง

**หมายเหตุ**

ไม่แนะนำให้ใช้เพื่อการป้องกันก่อนการสัมผัส หรือป้องกันหลังการสัมผัส

4. Cidofovir sterile sol ง

*ยากำพร้า*

**เงื่อนไข**

1. ใช้กับผู้ป่วยที่มีภาวะติดเชื้อ adenovirus ในเลือดหรืออวัยวะอื่นที่มีอาการรุนแรงที่ไม่เป็นผู้ป่วยระยะสุดท้าย (terminally ill) โดยมีอาการทางคลินิกที่เข้าได้ ร่วมกับการตรวจวินิจฉัยข้อใดข้อหนึ่ง ดังต่อไปนี้
   1.1 การตรวจพบ adenovirus ในเลือดด้วยวิธีทางอนูพันธุศาสตร์ (molecular detection)
   1.2 การตรวจพบ adenovirus จากสิ่งส่งตรวจของอวัยวะที่มีอาการสงสัย ด้วยวิธีทางอนูพันธุศาสตร์ (molecular detection) เช่น ปัสสาวะ สารคัดหลั่งจากทางเดินหายใจส่วนล่าง น้ำล้างจากถุงลมปอด (bronchoalveolar lavage fluid)
   1.3 การตรวจพบลักษณะทางพยาธิวิทยาที่เข้าได้กับการติดเชื้อ adenovirus (cytopathological change) หรือการตรวจพบไวรัสจากการตรวจด้วยกล้อง electron microscope
2. ใช้ในกรณีพิเศษตามคำแนะนำของแพทย์ผู้เชี่ยวชาญด้านโรคติดเชื้อ

5. Ganciclovir sodium sterile pwdr ง

**เงื่อนไข**

1. ใช้สำหรับ cytomegalovirus disease
2. ใช้ในกรณีพิเศษตามคำแนะนำของแพทย์ผู้เชี่ยวชาญด้านโรคติดเชื้อ

6. Peramivir sterile sol ง

*ยากำพร้า*

**เงื่อนไข**

ใช้กับผู้ป่วยโรคไข้หวัดใหญ่ที่มีอาการรุนแรงและไม่สามารถใช้ยาชนิดกิน หรือชนิดสูดพ่นได้

## 5.3.2 Antiretrovirals

ยากลุ่มนี้เป็นยาตามนโยบายเอดส์แห่งชาติของกรมควบคุมโรค สำนักงานประกันสังคม สำนักงานหลักประกันสุขภาพแห่งชาติ และกรมบัญชีกลาง

| | | | |
|---|---|---|---|
| 1. | Efavirenz (EFV) | cap, tab | ก |
| 2. | Lamivudine (3TC) | tab, syr | ก |
| 3. | Nevirapine (NVP) | tab, susp | ก |

**หมายเหตุ**

จะนำรูปแบบ tab ออกจากบัญชี ในรอบการพิจารณาถัดไป เนื่องจากปัจจุบันอยู่ระหว่างการเปลี่ยนผ่านการใช้ยาตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564

| | | | |
|---|---|---|---|
| 4. | Tenofovir disoproxil fumarate (TDF) | tab | ก |
| 5. | Tenofovir disoproxil fumarate + Emtricitabine (TDF + FTC) | tab (300 + 200 mg) | ก |
| 6. | Tenofovir disoproxil fumarate + Emtricitabine + Efavirenz (TDF + FTC + EFV) | tab (300 + 200 + 600 mg) | ก |
| 7. | Tenofovir disoproxil fumarate + Lamivudine + Dolutegravir sodium (TDF + 3TC + DTG) | tab (300 + 300 + 50 mg) | ก |

**หมายเหตุ**

ยาเม็ดสูตรผสม Tenofovir disoproxil fumarate + Lamivudine + Dolutegravir sodium ขนาด 300 + 300 + 50 mg ที่มีราคาเสนอเข้าสู่บัญชียาหลักแห่งชาติเม็ดละไม่เกิน 23.33 บาท (ราคารวมภาษีมูลค่าเพิ่ม) กำหนดยืนราคา 732 วัน นับจากวันที่ 19 สิงหาคม 2564 เงื่อนไข และรายละเอียดอื่น ๆ ให้ดูตามแบบเสนอยาในเว็บไซต์ http://ndi.fda.moph.go.th/drug_national/

| | | | |
|---|---|---|---|
| 8. | Zidovudine (AZT) | cap, oral sol | ก |
| 9. | Zidovudine + Lamivudine (AZT + 3TC) | tab (เฉพาะ 300+150 mg) | ก |
| 10. | Zidovudine + Lamivudine + Nevirapine (AZT + 3TC + NVP) | tab (เฉพาะ 250+150+200 mg) | ก |

**หมายเหตุ**

จะนำออกจากบัญชี ในรอบการพิจารณาถัดไป เนื่องจากปัจจุบันอยู่ระหว่างการเปลี่ยนผ่านการใช้ยาตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564

11. Rilpivirine (RPV) tab ข

**หมายเหตุ**

ใช้ยานี้ตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564

12. Atazanavir sulfate (ATV) cap ค

**หมายเหตุ**

จะนำออกจากบัญชี ในรอบการพิจารณาถัดไป เนื่องจากปัจจุบันอยู่ระหว่างการเปลี่ยนผ่านการใช้ยาตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564

13. Dolutegravir (DTG) tab (เฉพาะ 50 mg) ค

**หมายเหตุ**

1. ใช้ยานี้ตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564
2. ผู้ป่วยเดิมที่ดื้อยาควรปรึกษาแพทย์ผู้เชี่ยวชาญก่อนสั่งใช้ยานี้
3. ยาเม็ด Dolutegravir ขนาด 50 mg ที่มีราคาเสนอเข้าสู่บัญชียาหลักแห่งชาติเม็ดละไม่เกิน 21.33 บาท (ราคารวมภาษีมูลค่าเพิ่ม) กำหนดยืนราคา 732 วัน นับจากวันที่ 19 สิงหาคม 2564 เงื่อนไข และรายละเอียดอื่น ๆ ให้ดูตามแบบเสนอยาในเว็บไซต์ http://ndi.fda.moph.go.th/drug_national/

14. Lopinavir + Ritonavir (LPV + RTV) tab, oral sol ค

**หมายเหตุ**

จะนำรูปแบบ tab ออกจากบัญชี ในรอบการพิจารณาถัดไป เนื่องจากปัจจุบันอยู่ระหว่างการเปลี่ยนผ่านการใช้ยาตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564

15. Ritonavir (RTV) tab, oral sol ค

16. Abacavir (ABC) tab ค

**เงื่อนไข**

1. ใช้กับผู้ป่วยที่ไม่สามารถใช้ยา tenofovir หรือเกิดผลข้างเคียงที่ไม่สามารถใช้ยา tenofovir ได้ (ยา tenofovir ผลข้างเคียงที่สำคัญคือ ผลต่อไต และผลต่อ bone density)
2. ใช้เป็น nucleoside reverse transcriptase inhibitor (NRTI) ในสูตรยาต้านไวรัสดื้อยา ในกรณีที่การรักษาล้มเหลวจากเชื้อดื้อยาต้านไวรัสสูตรก่อน โดยต้องมีผลการตรวจ genotypic resistance ที่ไวกับยา abacavir และเชื้อไวต่อยาอื่นในสูตรอย่างน้อย 2 ชนิด
3. ใช้กับเด็กที่ติดเชื้อเอชไอวีอายุ 3 เดือนขึ้นไป

**หมายเหตุ**

1. ผู้ป่วยที่ได้รับยา abacavir อาจมีภาวะ hypersensitivity ได้โดยเฉพาะใน 6 สัปดาห์แรก อาการส่วนใหญ่มักจะมีหลายระบบร่วมกัน หากพบอาการอย่างน้อย 2 ข้อดังต่อไปนี้

   1.1 ไข้

   1.2 ผื่น

   1.3 คลื่นไส้อาเจียน ท้องเสีย ปวดท้อง

   1.4 อ่อนเพลียมาก ปวดกล้ามเนื้อ ปวดข้อ (arthralgia)

   1.5 หอบเหนื่อย ไอ เจ็บคอ

   ให้หยุดยา abacavir ทันที และห้ามให้ยา abacavir อีก (ห้าม rechallenge) เพราะอาจจะทำให้ผู้ป่วยเสียชีวิตได้
2. การตรวจ HLA B*5701 ขึ้นกับดุลพินิจของแพทย์
3. ผู้ป่วยที่จะใช้ยานี้เป็นสูตรแรกควรมีค่า baseline HIV-1 RNA viral load น้อยกว่า 100,000 copies/ml (เนื่องจากยามีประสิทธิภาพน้อยกว่า tenofovir เมื่อให้ในผู้ป่วยที่มี baseline HIV-1 RNA viral load มากกว่า 100,000 copies/ml) หรือเป็นไปตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวีประเทศไทย ปี 2563/2564

17. Abacavir + Lamivudine (ABC + 3TC) tab (600 + 300 mg) ค

**เงื่อนไข**

1. ใช้กับผู้ป่วยที่ไม่สามารถใช้ยา tenofovir หรือเกิดผลข้างเคียงที่ไม่สามารถใช้ยา tenofovir ได้ (ยา tenofovir ผลข้างเคียงที่สำคัญคือ ผลต่อไต และผลต่อ bone density)
2. ใช้เป็น nucleoside reverse transcriptase inhibitor (NRTI) ในสูตรยาต้านไวรัสดื้อยา ในกรณีที่การรักษาล้มเหลวจากเชื้อดื้อยาต้านไวรัสสูตรก่อน โดยต้องมีผลการตรวจ genotypic resistance ที่ไวกับยา abacavir และเชื้อไวต่อยาอื่นในสูตรอย่างน้อย 2 ชนิด
3. ใช้กับเด็กที่ติดเชื้อเอชไอวีอายุ 3 เดือนขึ้นไป

**หมายเหตุ**

1. ผู้ป่วยที่ได้รับยา abacavir อาจมีภาวะ hypersensitivity ได้โดยเฉพาะใน 6 สัปดาห์แรก อาการส่วนใหญ่มักจะมีหลายระบบร่วมกัน หากพบอาการอย่างน้อย 2 ข้อดังต่อไปนี้

   1.1 ไข้

   1.2 ผื่น

   1.3 คลื่นไส้อาเจียน ท้องเสีย ปวดท้อง

   1.4 อ่อนเพลียมาก ปวดกล้ามเนื้อ ปวดข้อ (arthralgia)

   1.5 หอบเหนื่อย ไอ เจ็บคอ

   ให้หยุดยา abacavir ทันที และห้ามให้ยา abacavir อีก (ห้าม rechallenge) เพราะอาจจะทำให้ผู้ป่วยเสียชีวิตได้
2. การตรวจ HLA B*5701 ขึ้นกับดุลพินิจของแพทย์
3. ผู้ป่วยที่จะใช้ยานี้เป็นสูตรแรกควรมีค่า baseline HIV-1 RNA viral load น้อยกว่า 100,000 copies/ml (เนื่องจากยามีประสิทธิภาพน้อยกว่า tenofovir เมื่อให้ในผู้ป่วยที่มี baseline HIV-1 RNA viral load มากกว่า 100,000 copies/ml) หรือเป็นไปตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวีประเทศไทย ปี 2563/2564

| | | | |
|---|---|---|---|
| 18. | Darunavir (DRV) | tab (เฉพาะ 300, 600 และ 800 as base) | ค |

**เงื่อนไข**

ใช้รักษาโรคติดเชื้อเอชไอวีที่ดื้อต่อยาสูตรพื้นฐาน และสูตรที่สอง โดยเป็นไปตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564

| | | | |
|---|---|---|---|
| 19. | Raltegravir (RAL) | tab (เฉพาะ 400 mg) | จ(2) |

**เงื่อนไข**

1. ใช้รักษาโรคติดเชื้อเอชไอวีที่ดื้อต่อยาสูตรพื้นฐาน และสูตรที่สอง ในกรณีที่ไม่สามารถเข้าถึงยา DTG ได้ โดยมีแนวทางกำกับการใช้ยาเป็นไปตามรายละเอียดในภาคผนวก 3
2. ใช้ในหญิงตั้งครรภ์ที่มีความเสี่ยงสูงทั้ง 2 กลุ่ม ในกรณีที่ไม่สามารถเข้าถึงยา DTG ได้ โดยมีเงื่อนไขดังนี้
   2.1 **กลุ่มที่ 1** หญิงตั้งครรภ์ที่ไม่เคยได้รับยาต้านเอชไอวีมาก่อน และจะเริ่มยาต้านไวรัสหลังอายุครรภ์ 32 สัปดาห์ โดยมีแนวทางกำกับการใช้ยาเป็นไปตามรายละเอียดในภาคผนวก 3
   2.2 **กลุ่มที่ 2** หญิงตั้งครรภ์ที่เคยได้รับยาต้านเอชไอวีมาก่อนแต่ระดับไวรัสในพลาสมา (plasma viral load) ที่อายุครรภ์มากกว่า 32 สัปดาห์ >1,000 copies/ml โดยมีแนวทางกำกับการใช้ยาเป็นไปตามรายละเอียดในภาคผนวก 3

**หมายเหตุ**

จะนำออกจากบัญชี เมื่อยา dolutegravir มี availability เพียงพอแล้ว เนื่องจากปัจจุบันอยู่ระหว่างการเปลี่ยนผ่านการใช้ยาตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564