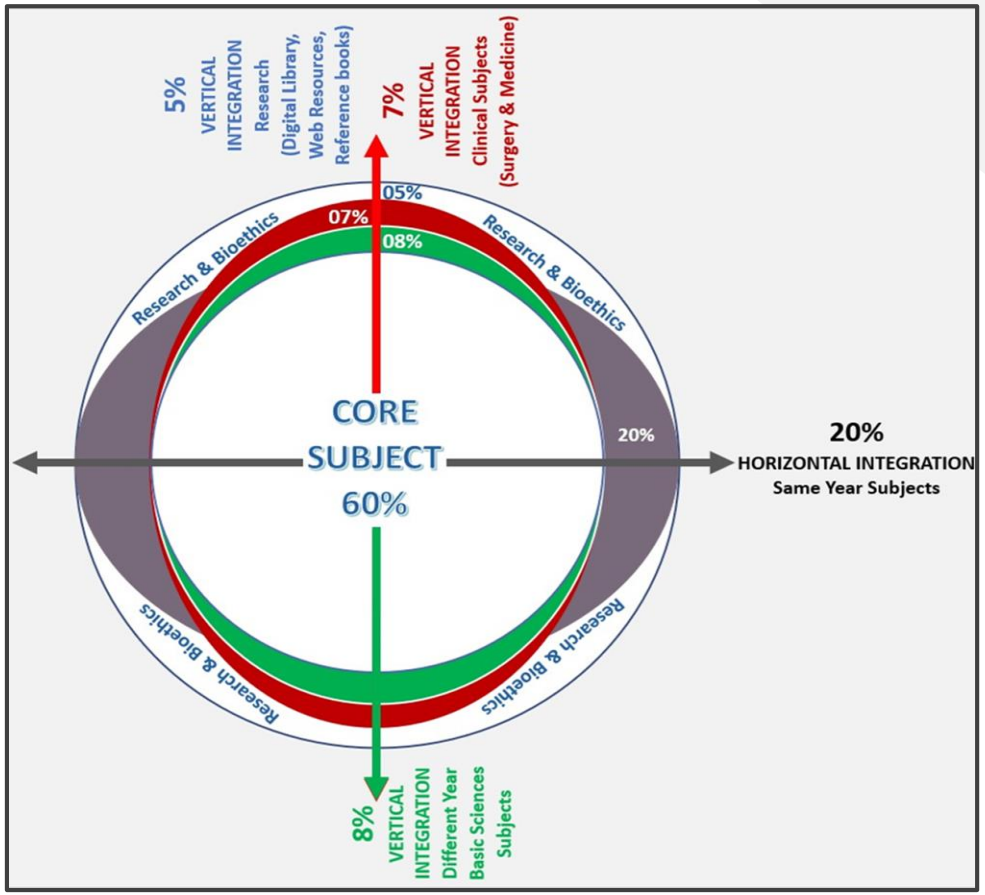
ANTI-VIRAL DRUGS

UMAR'S MODEL OF INTEGRATION

3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	



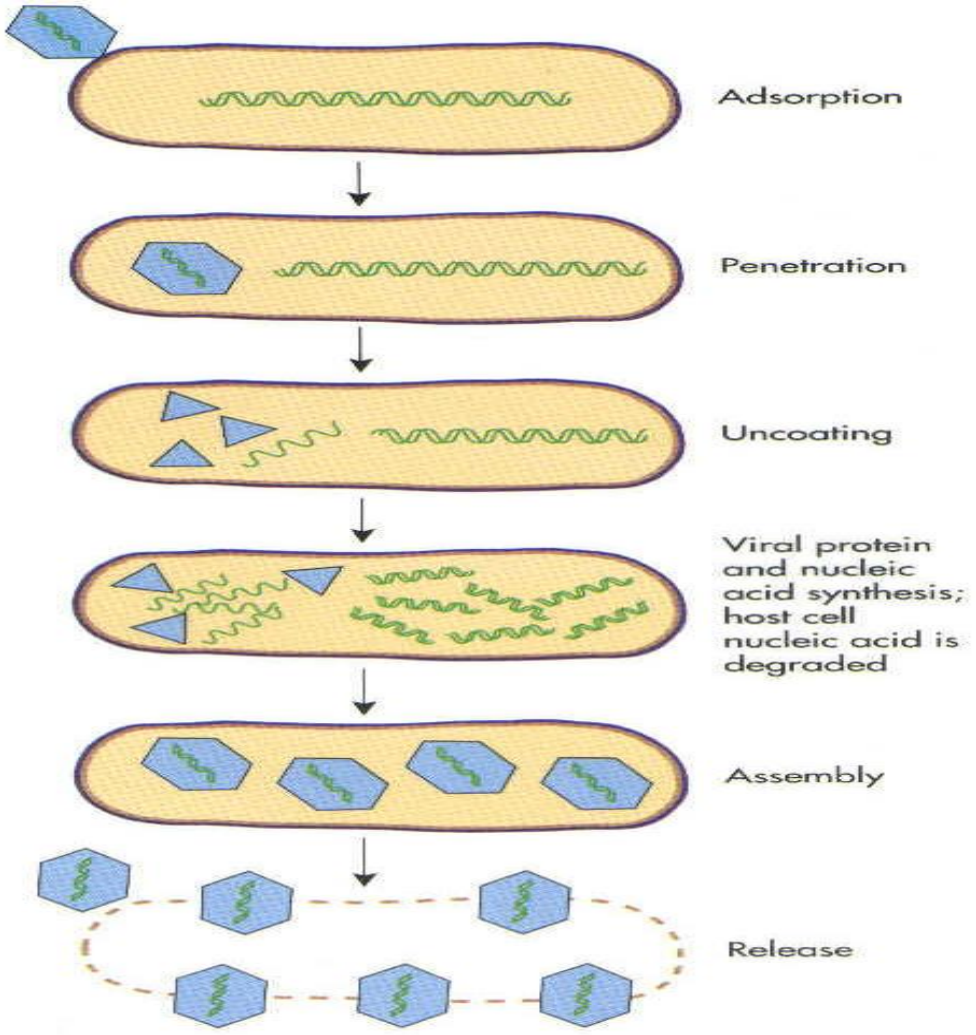
LEARNING OBJECTIVES

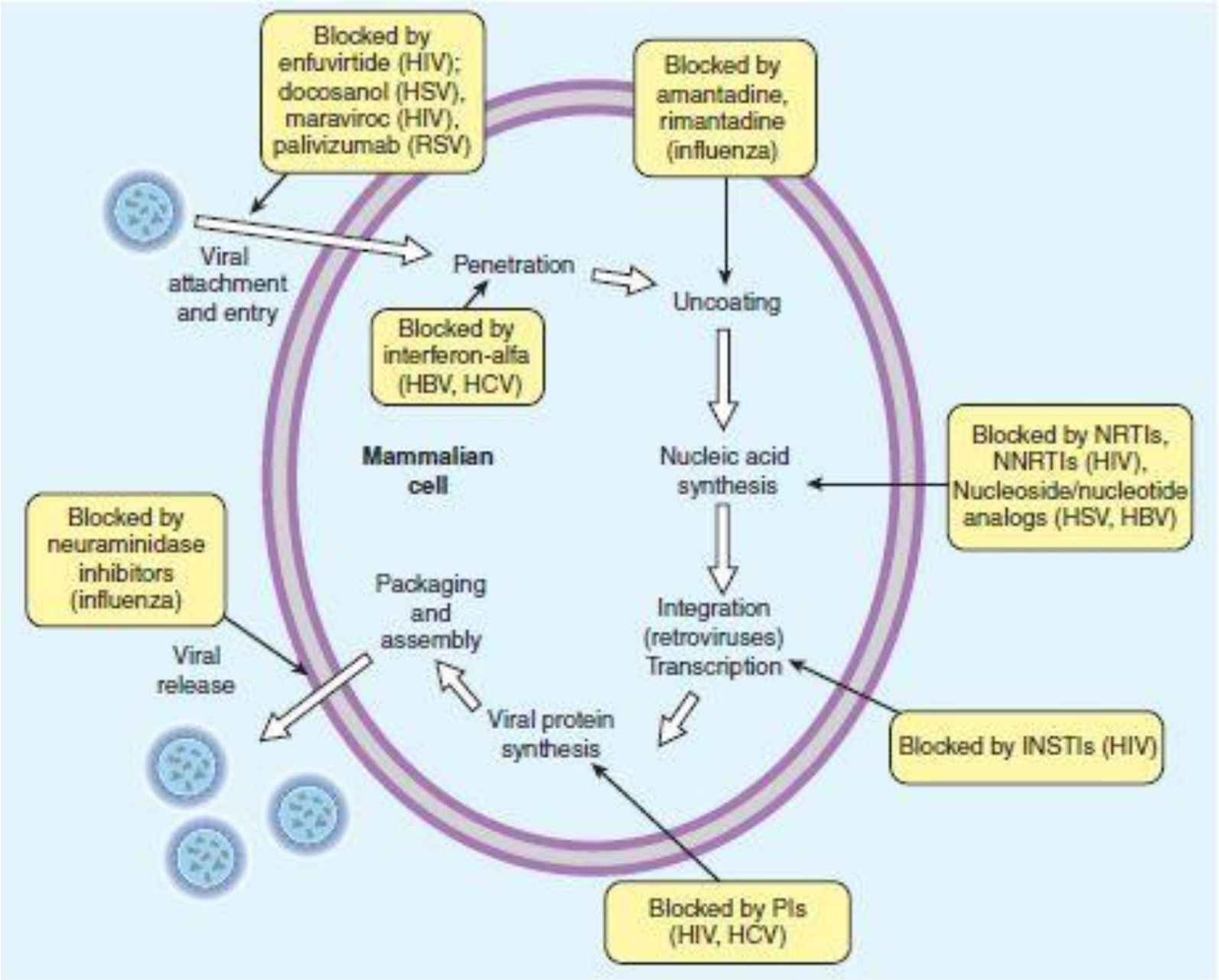
At the end of the lecture, students will be able to:

- Recall life cycle of viruses
- Classify antiviral drugs according to action on virus replication
- Classify antiviral drugs according to viral diseases
- Outline the salient pharmacokinetic & pharmacodynamic features of antiviral drugs used to treat HSV, VZV & CMV and influenza infections
- Define HAART
- Describe the mechanism of action of major drug groups used in AIDS

VIRAL REPLICATION & DRUG TARGETS

- Cell entry
  - Attachment
  - Penetration
- Uncoating/dismantling
- Viral nucleic acid and protein synthesis
- Post-translational modifications
- Assembly of virion components
- Release of virions




Blocked by enfuvirtide (HIV); docosanol (HSV), maraviroc (HIV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Mammalian cell
Nucleic acid synthesis
Blocked by NRTIs, NNRTIs (HIV), Nucleoside/nucleotide analogs (HSV, HBV)
Blocked by neuraminidase inhibitors (influenza)
Packaging and assembly
Integration (retroviruses) Transcription
Viral release
Viral protein synthesis
Blocked by INSTIs (HIV)
Blocked by PIs (HIV, HCV)

ANTI-VIRAL AGENTS

CLASSIFICATION

MECHANISM OF ACTION	DRUGS
Drugs that inhibit attachment to host cells	Maraviroc (HIV),Docosanol, palivizumab
Drugs that block penetration	Enfuvirtide (HIV)
Drugs that inhibit un coating of viral DNA	Amantadine,rimantadine
Drugs that inhibit viral nucleic acid synthesis	DNA polymerase inhibitors, Nucleoside & non-nucleoside reverse transcriptase inhibitors, Acyclovir
Drugs that inhibit late protein synthesis	Protease inhibitors
Drugs that inhibit release of viruses	Neuraminidase inhibitors
Immunomodulators	Interferons

ANTI-VIRAL AGENTS

CLASSIFICATION

1. Agents to treat HSV & VZV infections

- Acyclovir & Valacyclovir
- Famciclovir & Penciclovir
- Trifluridine
- Docosanol
- Idoxuridine
- Vidarabine
- *Foscarnet, Cidofovir (Acyclovir resistant infection only)

Investigational Agent — Valomaciclovir
Pritelivir
Amenamevir

ANTI-VIRAL AGENTS

FR

CLASSIFICATION

2. Agents to treat CMV infections

- Ganciclovir & Valganclovir
- Cidofovir
- Foscarnet
- Fomivirisen
- Leteromavir

Investigational Agent : Marabravir, Brincidofovir

3. Anti-influenza agents

- Amantidine & Rimantadine
- Oseltamivir, Zanamivir & Peramivir
- Baloxavir Marboxil

Investigational Agent :Laninamivir octanoate

ANTI-VIRAL AGENTS

FR

CLASSIFICATION

4. Anti-Retroviral agents

A. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Zidovudine
- Didanosine
- Lamivudine
- Stavudine
- Zalcitabine
- Abacavir
- Emtricitrabine
- Tenofovir

ANTI-VIRAL AGENTS

CLASSIFICATION

4. Anti-Retroviral agents

B. Non-nucleoside Reverse Transcriptase inhibitors

- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine
- Rilpivirine

C. Protease Inhibitors

- Atazanavir
- Saquinavir
- Ritonavir
- Tipranavir
- Indinavir
- Nelfinavir

Darunavir
Lopinavir
Fosamprenavir

ANTI-VIRAL AGENTS

CLASSIFICATION

4. Anti-Retroviral agents

D. Integrase Strand Transfer Inhibitors

- Raltegravir
- Elvitegravir
- Dolutegravir

E. Fusion Inhibitors

- Enfirvitide

F. Entry Inhibitors

- Maraviroc

5. Agents used against Respiratory syncytial virus

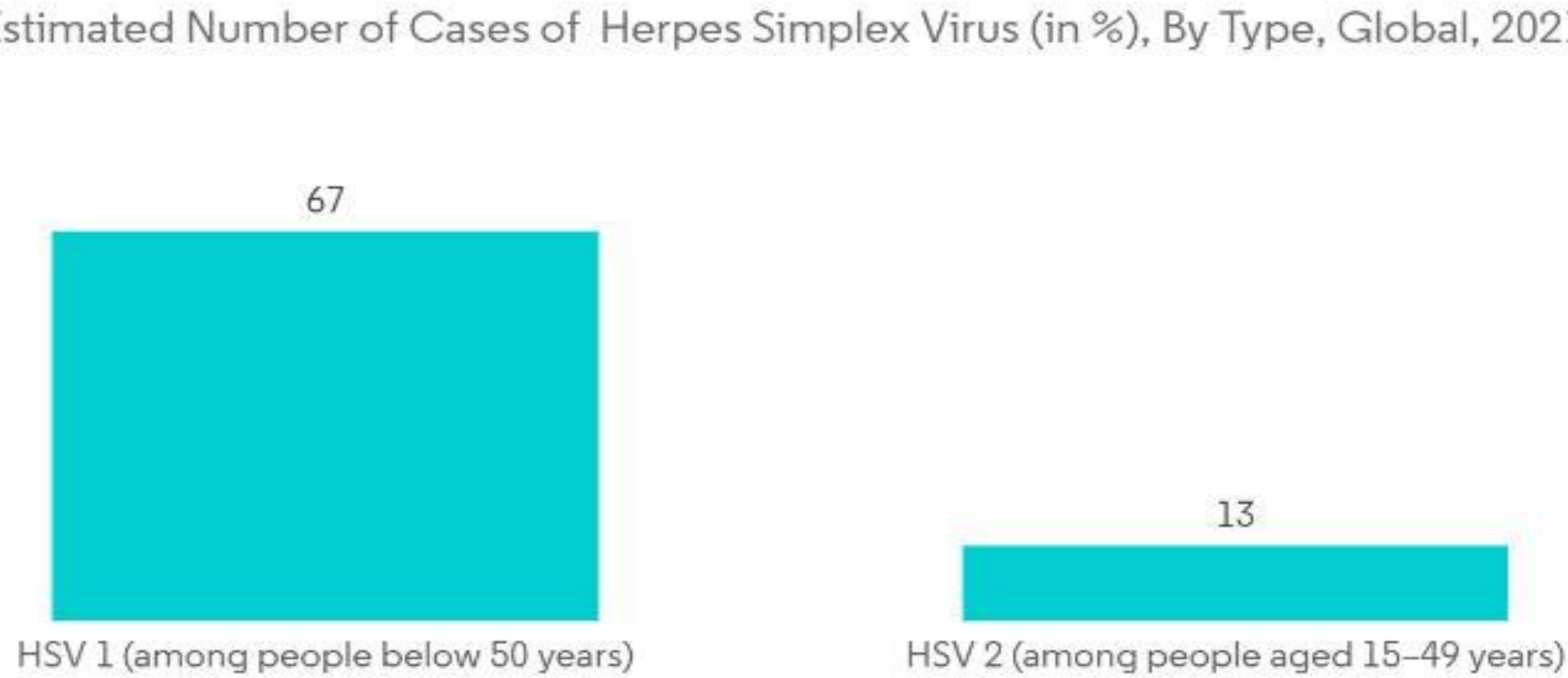
- Ribavirin
- Palivizumab

6. Agents used against Corona Virus (COVID-19)

- Remdesvir

ANTI HERPES AGENTS

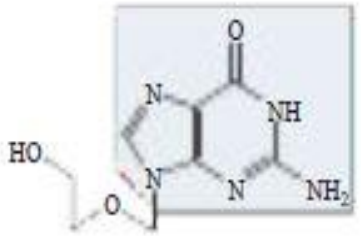
EPIDEMOLOGY OF HSV INFECTIONS



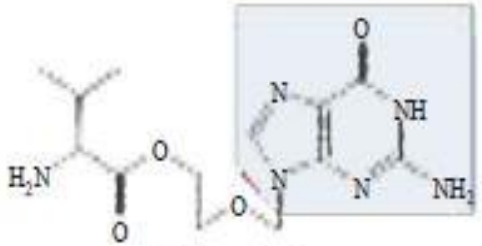
ANTI-HERPES AGENTS

CHEMISTRY

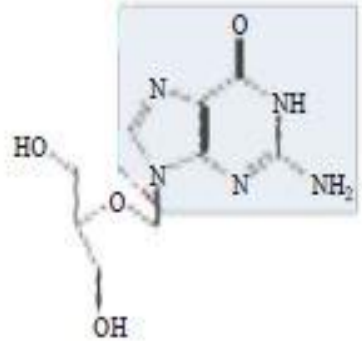
B Antiherpesvirus nucleoside and nucleotide analogues



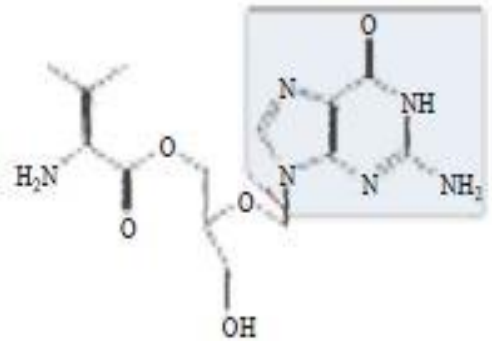
Acyclovir



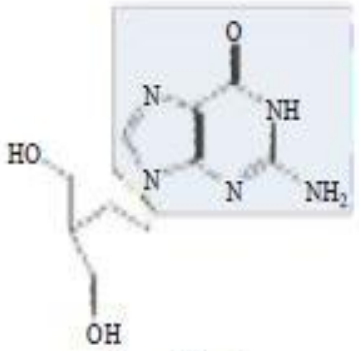
Valacyclovir
(prodrug)



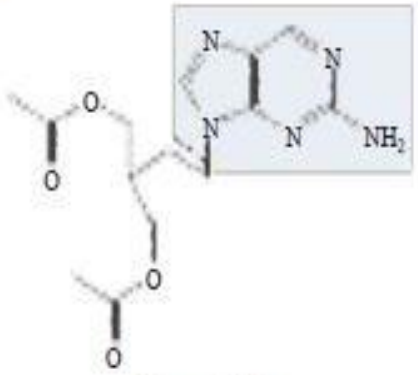
Ganciclovir



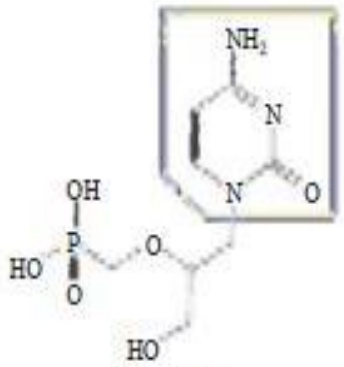
Valganciclovir
(prodrug)



Penciclovir

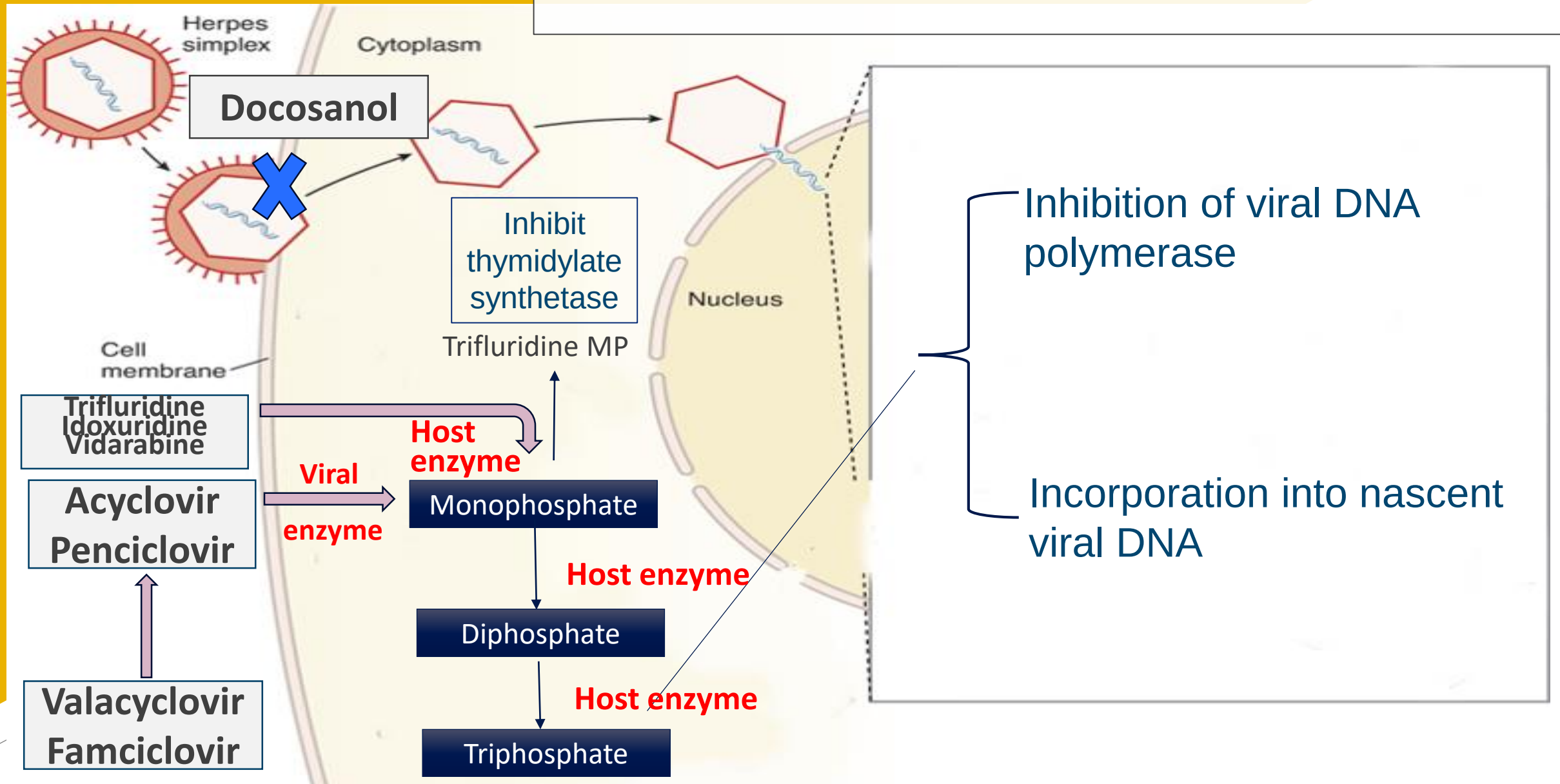


Famciclovir
(prodrug)



Cidofovir

MECHANISM OF ACTION



ANTI-HERPES AGENTS

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MECHANISM OF ACTION

- Taken up by host cells
- Most converted by viral (selective) and cellular (host) enzymes to the active triphosphate form
- The triphosphate causes viral nucleic acid inhibition by:
  i. Competition with natural nucleotides for access to DNA polymerase
  ii. Incorporation into nascent DNA .Chain termination is the characteristic of acyclovir (lack the 3′-hydroxyl group required for attachment of the next nucleoside)
  iii. Acyclovir terminated DNA bind the viral DNA polymerase irreversibly and prevents further replication activity **(SUICIDE INACTIVATION)**
- **Viral resistance**
  Viral kinases (Valacyclovir and famciclovir) (production & specificity)
  DNA polymerase

ANTI-HERPES AGENTS

ACYCLOVIR & ITS CONGENERS

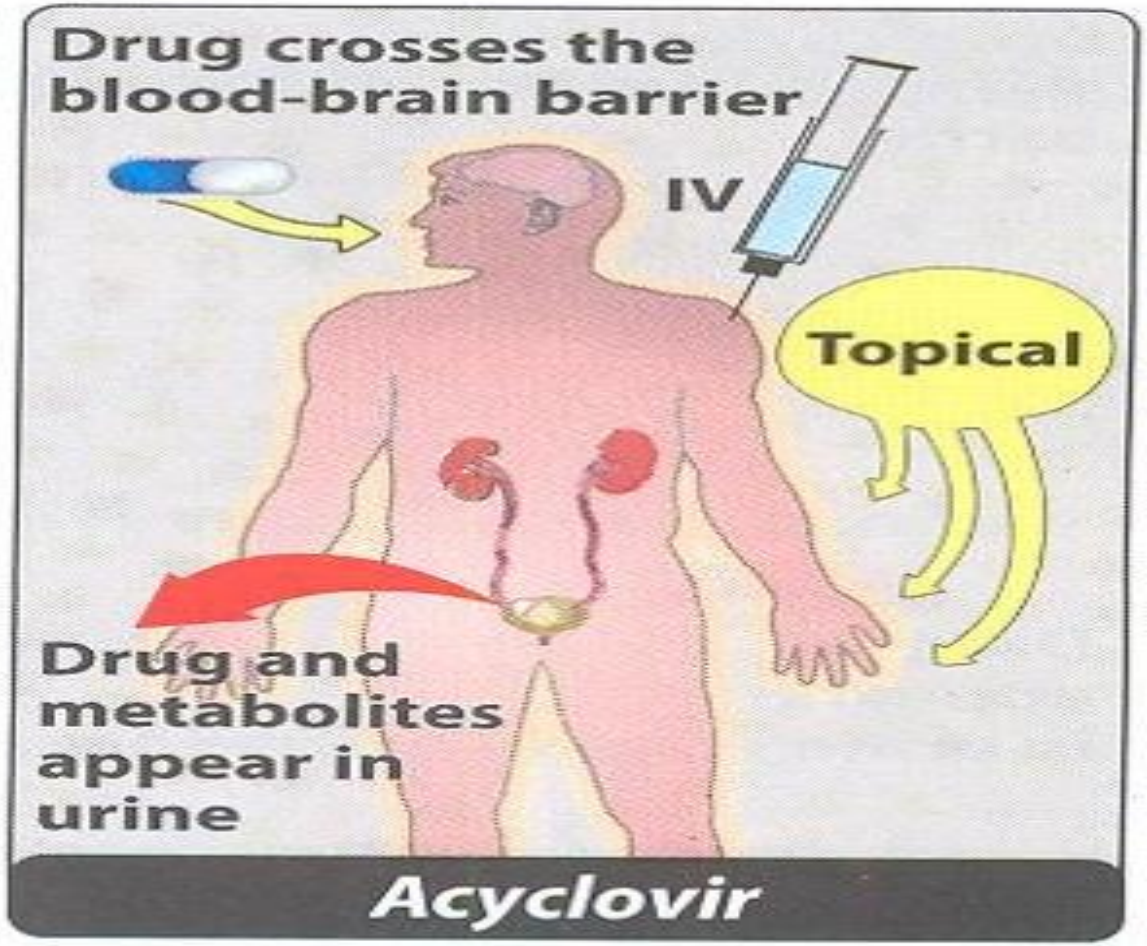
- **Valacyclovir** is a prodrug of **Acyclovir** with better bioavailability (valacyclovir is a prodrug that is rapidly converted to acyclovir by intestinal and hepatic enzymes and is more completely absorbed than acyclovir. Because of its greater bioavailability (55%), valacyclovir requires less frequent administration than acyclovir)
- **Famciclovir** is hydrolyzed to **Penciclovir** and has greatest bioavailability (70%)
- **Penciclovir** is used only topically and intravenously whereas **Famciclovir** can be administered orally

ANTI-HERPES AGENTS

FR

PHARMACOKINETICS

- Orally, I/V or topically (drops & cream)
- Oral B.A 15-20%
- $t_{1/2}$ = 3 hrs
- Distribution widely distributed, diffuses tissues and body fluids and CSF
- Partially metabolize to inactive product
- Excreted by kidney by GF and partly by tubular secretion



THERAPEUTIC USES

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Herpes Simplex Virus			
Genital herpes			
First episode	Acyclovir	PO[c]	400 mg tid *or* 200 mg 5×/day for 7-10 days
	Famciclovir	PO	250 mg tid for 7-10 days
	Valacyclovir	PO	1 g bid for 7-10 days
Recurrent	Acyclovir	PO	800 mg tid for 2 days *or* 400 mg tid *or* 200 mg 5×/day *or* 800 mg bid for 5 days
	Famciclovir	PO	125 mg bid for 5 days *or* 1000 mg repeated once at 12 hr for 1 day
	Valacyclovir	PO	500 mg bid for 3 days *or* 1 g/day for 5 days
Suppression[d]	Acyclovir	PO	400 mg bid *or* 200 mg tid
	Famciclovir	PO	250 mg bid
	Valacyclovir	PO	500 mg/day *or* 1 g/day (≥10 episodes/yr) *or* 250 mg bid
Encephalitis	Acyclovir[e]	IV	10-15 mg/kg/8 hr in 1-hr infusions for 14-21 days
Mucocutaneous disease in immunocompromised hosts	Acyclovir[f]	IV	5 mg/kg/8 hr for 7-14 days[g]
		PO	400 mg 5×/day for 7-14 days
	Valacyclovir[h]	PO	500 mg or 1 g bid for 7-10 days
	Penciclovir[h]	IV	5 mg/kg/8-12 hr for 7 days
	Famciclovir	PO	500 mg bid for 7-10 days
Orolabial herpes			
First episode	Acyclovir	PO	Children: 15 mg/kg 5×/day for 7 days (max. 200 mg/dose)
			Adults: Drugs and doses recommended for first-episode genital herpes have been used
Recurrent	Penciclovir 1%	Topical	Apply cream for 4 days q2h while awake
	Acyclovir 5%	Topical	Apply cream 5×/day for 4 days
	Docosanol 10%	Topical	Apply cream 5×/day until healed
	Valacyclovir	PO	2 g repeated once at 12 hr
	Famciclovir	PO	1500 mg once *or* 750 mg repeated once at 12 hr
	Acyclovir	PO	400 mg tid/day for 5 days
Neonatal HSV	Acyclovir[i]	IV	10-20 mg/kg/8 hr for 14-21 days
Keratoconjunctivitis HSV	Trifluridine[j]	Topical	1 drop of 1% solution topically q2h, ≤9 drops/day
	Vidarabine	Topical	½-inch ribbon of 3% ointment 5×/day
Varicella-Zoster Virus			
Varicella in normal children	Acyclovir	PO	20 mg/kg (≤800 mg) qid for 5 days
Varicella in immunocompromised hosts	Acyclovir	IV	10 mg/kg/8 hr *or* 500 mg/m^2/8 hr for 7-10 days[k]
Herpes zoster in immunocompromised hosts	Acyclovir	IV	10 mg/kg/8 hr in 1-hr infusion for 7-10 days[k]
Herpes zoster in normal hosts	Acyclovir	PO	800 mg 5×/day for 7-10 days
	Valacyclovir	PO	1 g tid for 7 days
	Famciclovir	PO	500 mg tid for 7 days
	Brivudin[h]	PO	120 mg daily for 7 days

ANTI-HERPES AGENT

ADVERSE EFFECTS

Nausea, vomiting (increase incidence with high doses of valacyclovir)

- Headache (Increase somnolence & lethargy with zidovudine)
- Hallucination & confusion in transplant pts (valacyclovir)

Local inflammation, renal damage & neurological toxicity (IV administration)

- Adequate hydration and avoid rapid infusion
- Avoid concomitant use of other nephrotoxic agents

Chromosomal & testicular atrophy(rats)

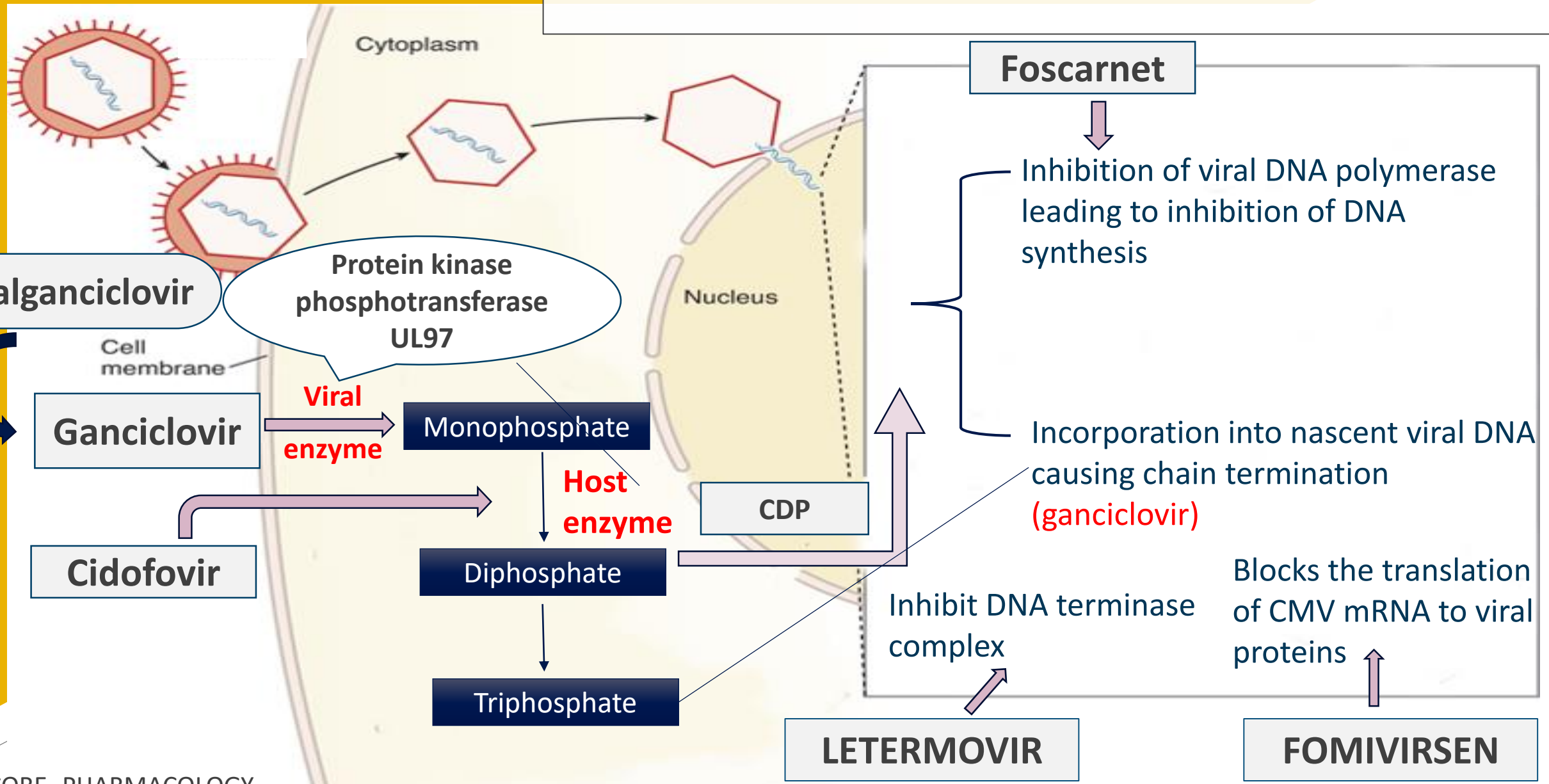
- Hematological complications(valacyclovir)

Agents to treat CMV infections

NATURAL HISTORY OF HCMV INFECTION

- Primary infection occurs when an individual with no immunity against this virus becomes infected for the first time.
- Afterwards, the virus establishes latency from which it may reactivate (second type of infection).
- The third type of infection is called reinfection when contact with an infectious individual results in superinfection of someone who has already been infected, despite their possession of natural immunity

MECHANISM OF ACTION



PHARMACOKINETICS

FR

Ganciclovir	• Oral (poor BA**),IV**, intravitreal injection and implant, ophthalmic gel • CSF conc 50% of serum • T1/2 4 hours (16-24hrs) • Renal elimination
Foscarnet	• Oral (poor BA**),IV only, cream** (HSV infection) • CSF conc 43-67% of serum • T1/2 3-7hours (deposition in bone) • Renal elimination
Cidofovir	• IV only, topical gel (HSV mucocutaneous lesions) • T1/2 2.6hrs (17-65hrs) • CSF distribution poor • Renal elimination (active tubular secretion)

CLINICAL INDICATIONS

FR

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
Letermovir	Oral, intravenous	CMV prophylaxis (transplant patients)	480 mg once daily orally or IV over 1 hour
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

ADVERSE EFFECTS

Ganciclovir

- **Myelosuppression**(zidovudine,azathiopurine & mycophenolate mofetil)
- **Vitreous hemorrhage & retinal detachment**
- Nausea, diarrhea
- Headache, insomnia & peripheral neuropathy

Foscarnet

- Renal impairment (saline preloading & avoid nephrotoxic drugs)
- Electrolyte imbalance
- CNS toxicity
- Nausea,vomiting,anemia and raised liver enzymes

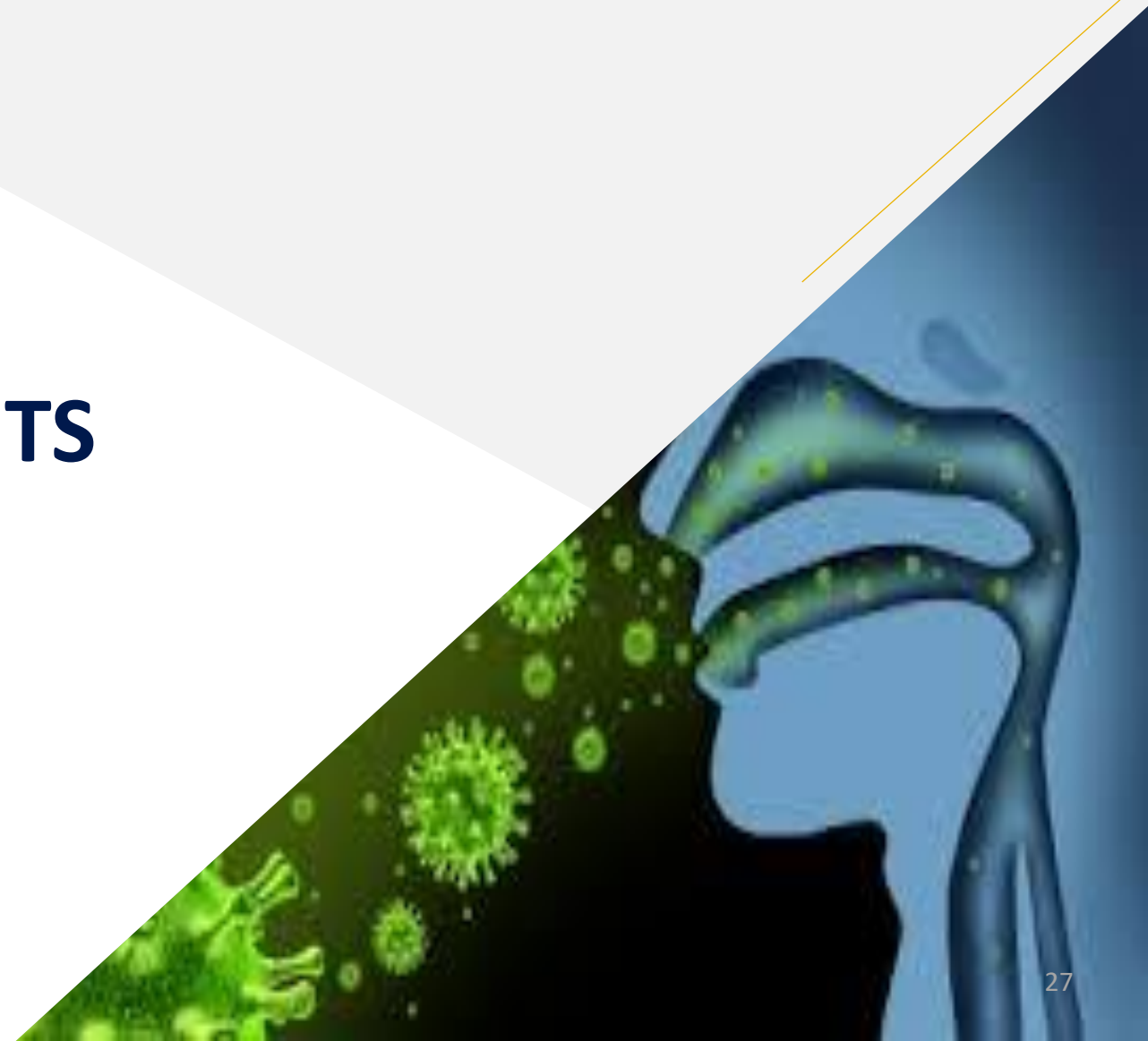
Cidofovir

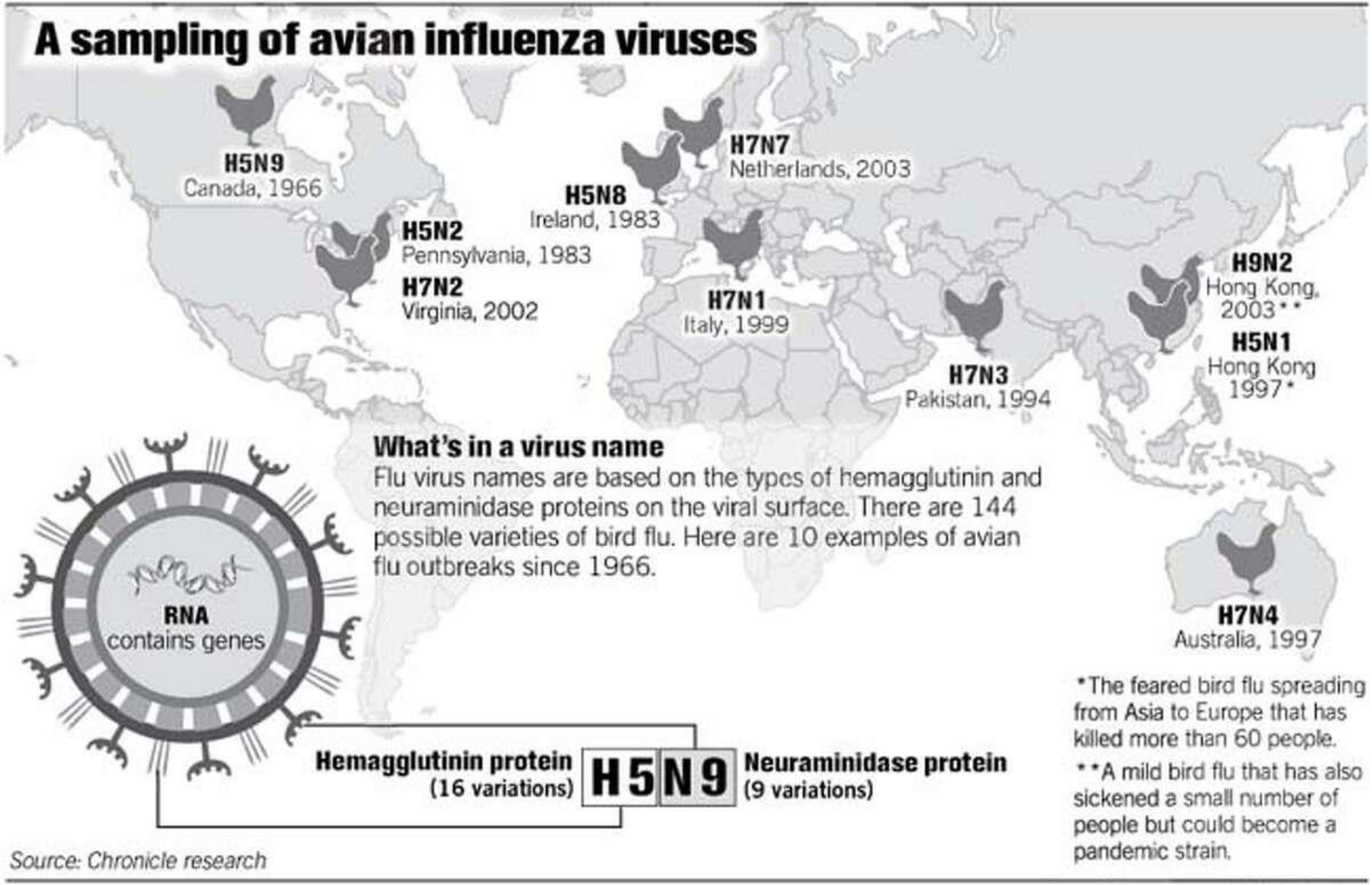
- **Nephrotoxicity**
- Uveitis & ocular hypotony
- Metabolic acidosis
- Neutropenia

FR

ANTI-INFLUENZA AGENTS

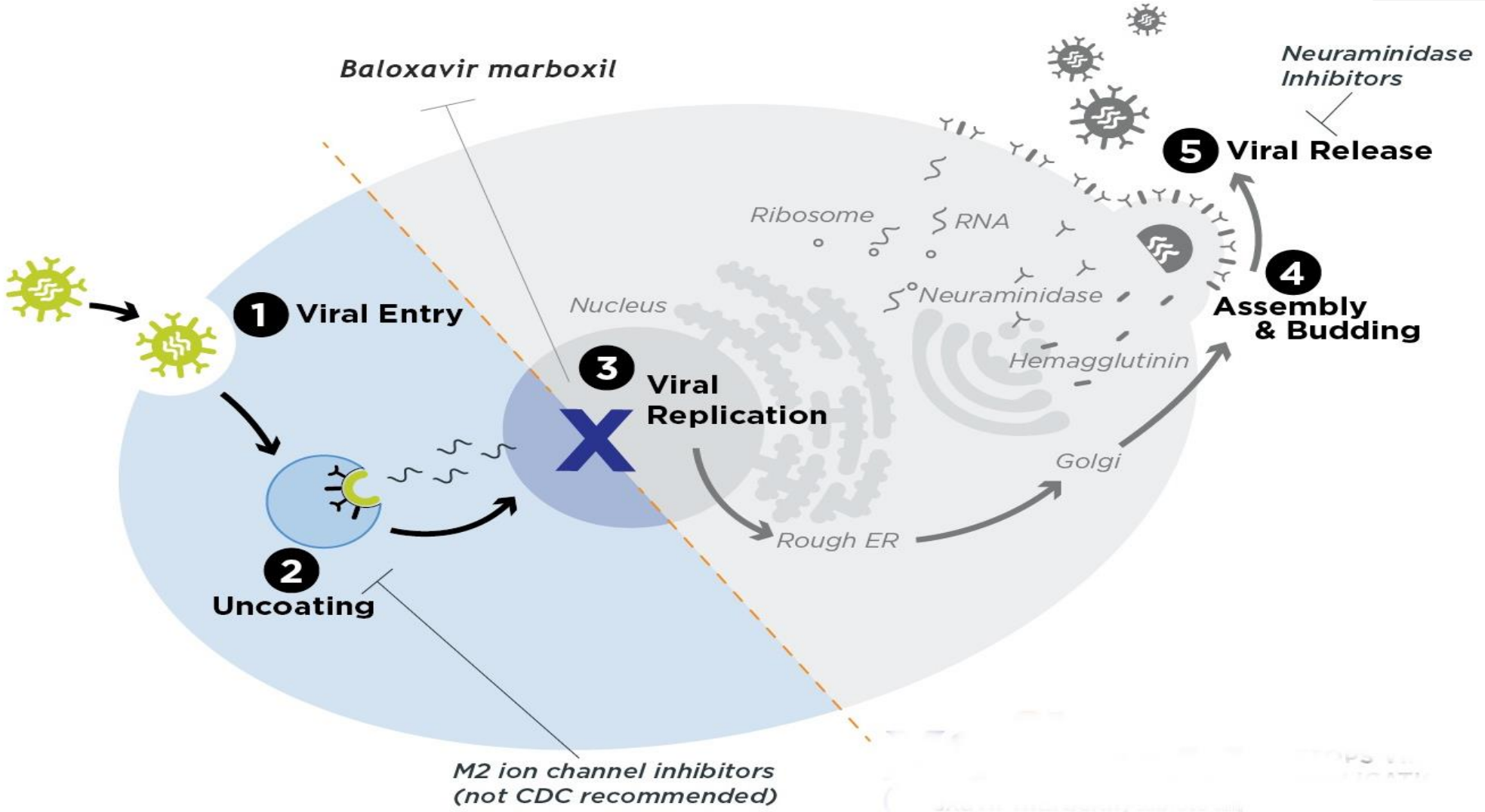
- Prophylaxis and active treatment





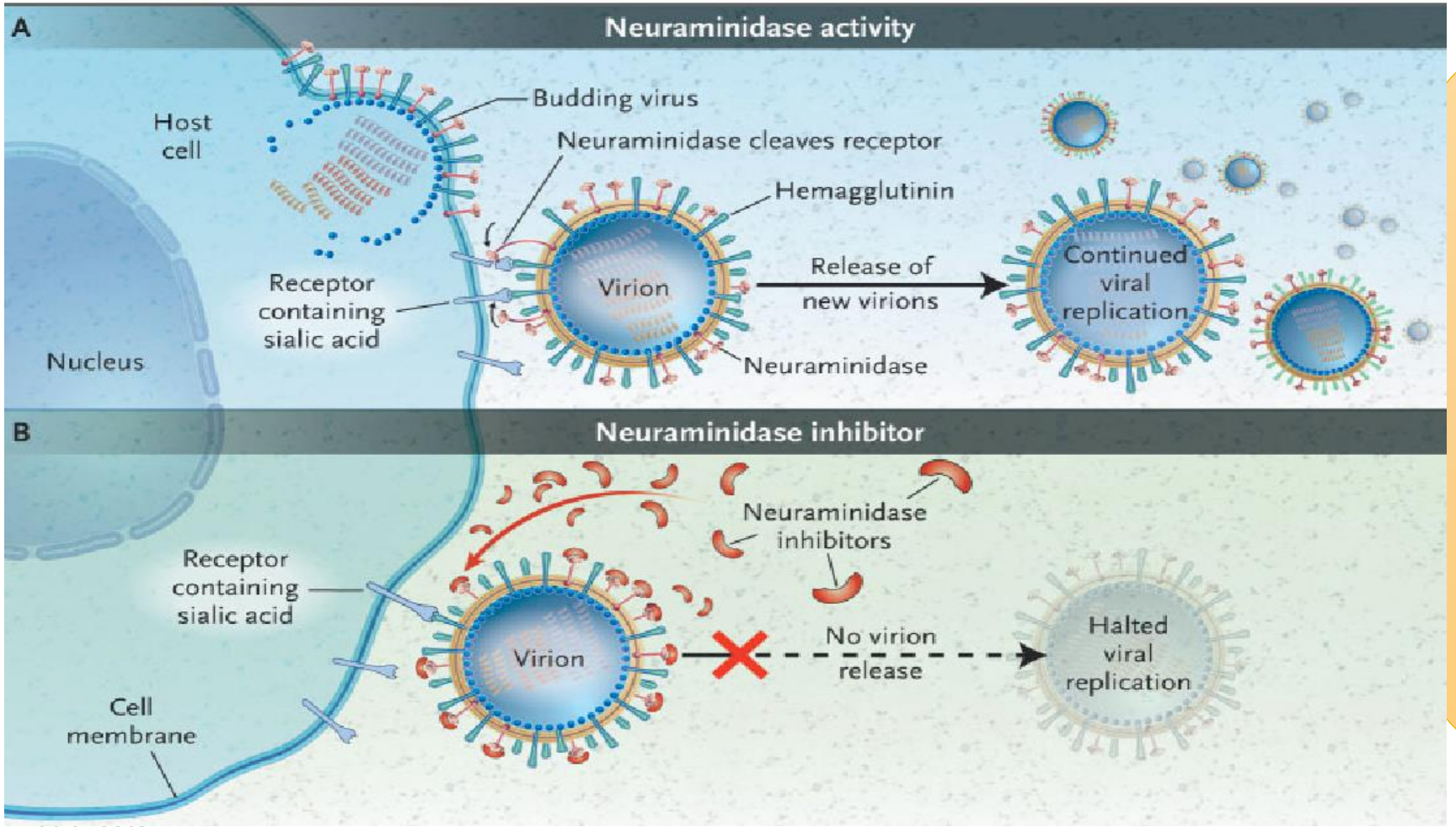
DRUGS USED IN INFLUENZA

SITE OF ACTION



OSELTAMIVIR & ZANAMIVIR

MECHANISM OF ACTION

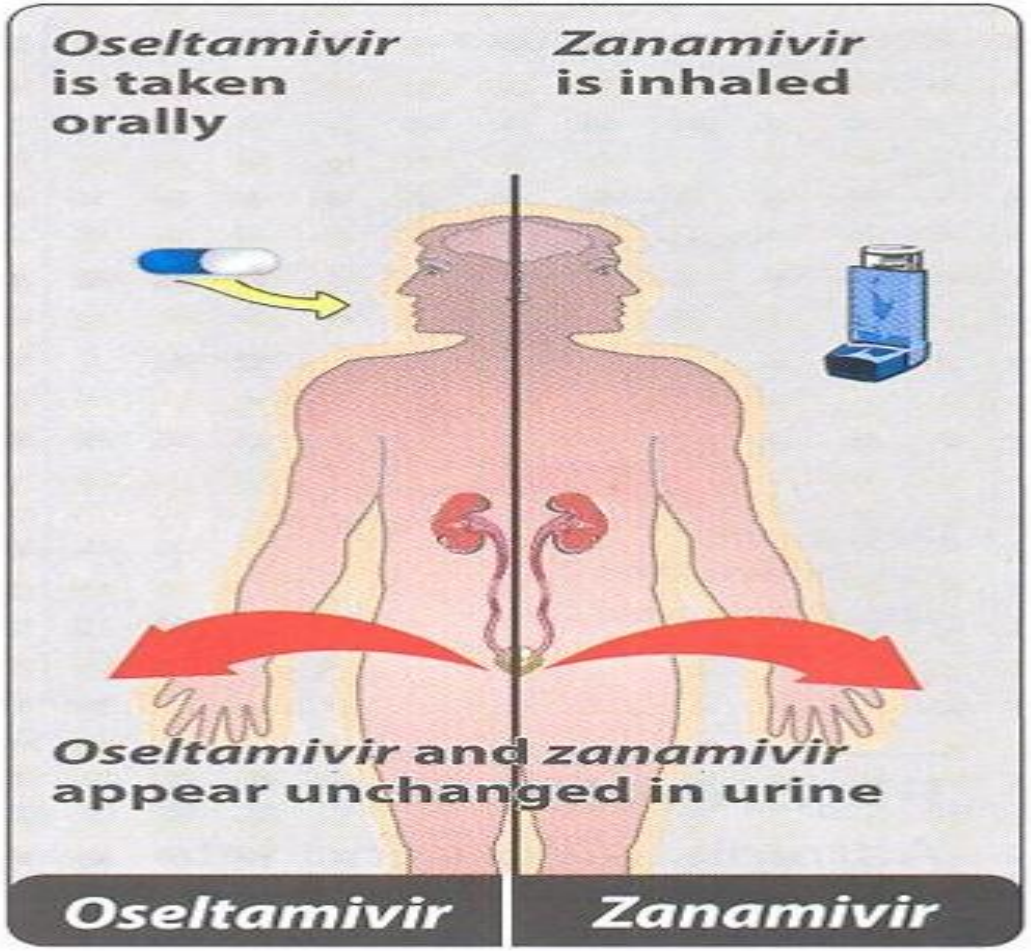


- Activity against both influenza A & B (H1N1,H2N2,H3N2, and the H5N1 avian influenza strain)
- Inhibit neuraminidase leading to clumping of newly released virions
- Inhibit the release of new progeny and viral spread

OSELTAMIVIR & ZANAMIVIR

PHARMACOKINETICS

- Oral BA 80%
- Prodrug metabolized by hepatic esterases to oseltamivir carboxylate
- t1/2 6-10hours
- Renal elimination



- Direct administration to lungs
- Conc in lungs> conc required for action
- t1/2 2.8 hours
- Renal elimination

OSELTAMIVIR & ZANAMIVIR

ADVERSE EFFECTS

Oseltamivir

- Nausea, vomiting & diarrhea (food)
- Headache
- Neuropsychiatric events

Zanamivir

- Cough
- Bronchospasm
- Nasal & throat discomfort

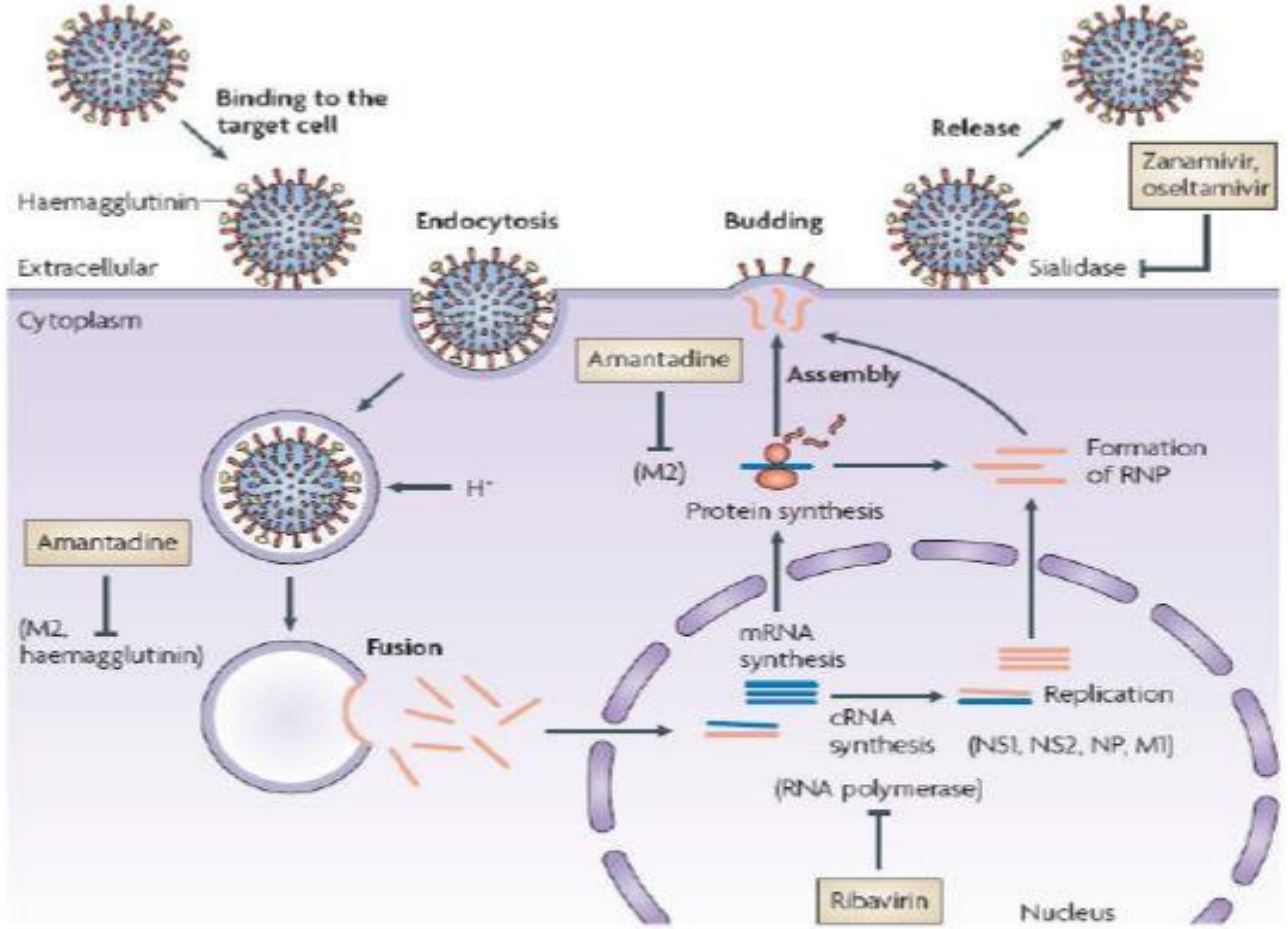
PERAMIVIR

NEURAMINIDASE INHIBITOR

- IV administration
- Renal elimination with half life of 20 hours
- Adverse effects include hypersensitivity skin reactions and neuropsychiatric events

AMANTADINE & RIMANTADINE

MECHANISM OF ACTION

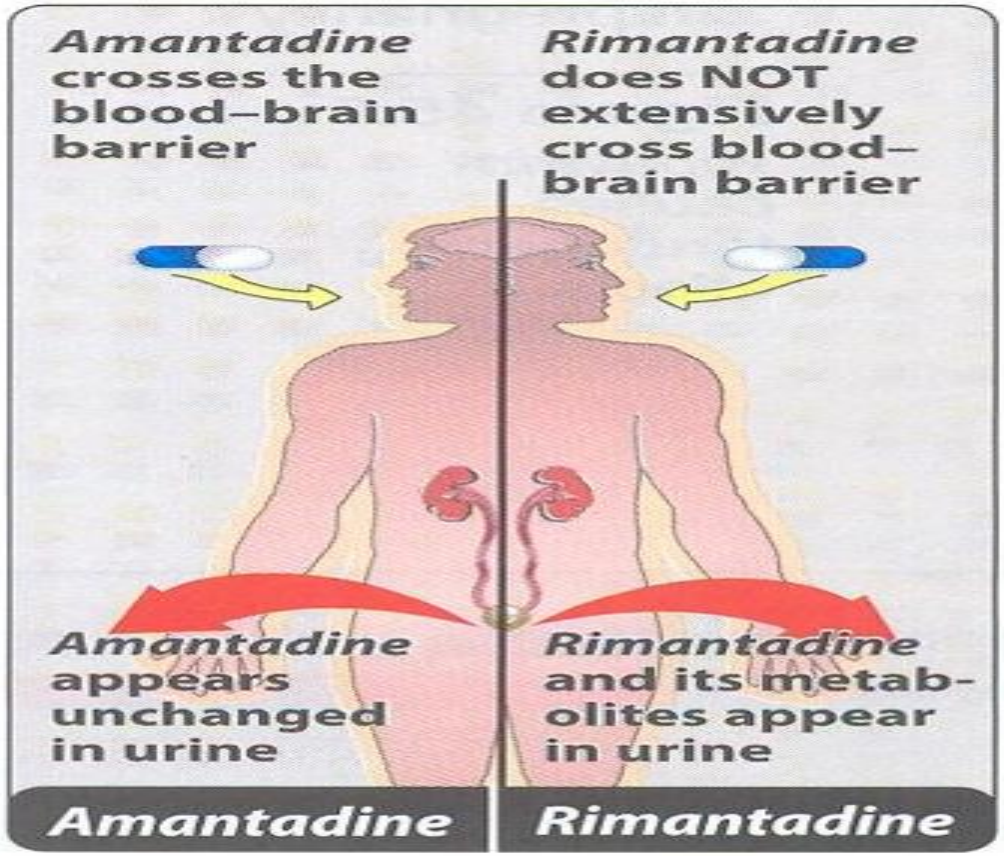


- Activity against influenza A
- Block M2 channel on virus leading to uncoating of viral RNA and preventing replication
- Rimantadine 4X active > amantadine

AMANTADINE & RIMANTIDINE

PHARMACOKINETICS

- Well absorbed orally
- Well distributed including CSF
- T1/2 12-18 hours
- Excreted unmetabolized in urine



- Good oral absorption
- CSF distribution less than amantadine
- T1/2 24-36hours
- Renal elimination by extensive metabolization

AMANTADINE & RIMANTADINE

ADVERSE EFFECTS

Gastrointestinal

- Nausea, vomiting ,anorexia

CNS

Amantadine > Rimantadine

- Nervousness, insomnia ,lightheadedness
- Behavioral changes, delirium, hallucinations & seizures (altered dopamine transmission)

BALOXAVIR MARBOXIL

ENDO NUCLEASE INHIBITOR

- Prodrug converted to active drug baloxavir
- Interferes with viral RNA transcription and blocks virus replication
- Oral administration
- Metabolized by UGT1A3 with half life of 80 hours

RESEARCH

Raglow Z, Kaul DR. A New Antiviral Option for Cytomegalovirus Prevention After Kidney Transplant.
JAMA. 2023;330(1):27–29. doi:10.1001/jama.2023.9100

Panda, K.; Parashar, D.; Viswanathan, R. An Update on Current Antiviral Strategies to Combat Human Cytomegalovirus Infection. *Viruses* **2023**, *15*, 1358. https://doi.org/10.3390/v15061358

BIOETHICS

- Experiencing emotional highs and lows that are potential adverse effects of immunosuppressive agents, such as corticosteroids
- Stress and challenges due to complex posttransplant regimens including multiple medications and complicated dosing schedules, routine monitoring of laboratory tests and drug levels, regular follow-up medical evaluations and laboratory tests, and lifestyle restrictions related to smoking, alcohol, and other potentially harmful substances
- Coping with physical changes and early complications, such as acute graft rejection
- Psychological acceptance of the transplant; for cadaver-donation recipients, this includes dealing with the circumstances that someone lost his/her life just when the transplant patient regained his/her own life
- Dealing with financial and economic issues, such as cost of transplant surgery, hospital stay, and/or follow-up care and medications

END OF LECTURE ASSESSMENT

1. Which of the following is not an important property of anti-viral drugs?

A. They are nucleoside/nucleotide prodrugs
B. They are activated inside infected host cells only
C. They use viral and host enzymes for activation
D. They don't require host immune system for their action
E. They use phosphorylation for activation

2. Which point in the replication cycle appears most easily blocked by antivirals?

A. Virus absorption
B. Virus penetration
C. Virus RNA and DNA replication
D. Virus protein synthesis
E. Exit of viruses from the cell

3. Choose the following correct combination of drug and virus:

A. Amantadine versus influenza B
B. Daclatasvir versus hepatitis C
C. Zidovudine versus hepatitis B
D. Saquinavir versus influenza A
E. Acyclovir versus HIV-AIDS