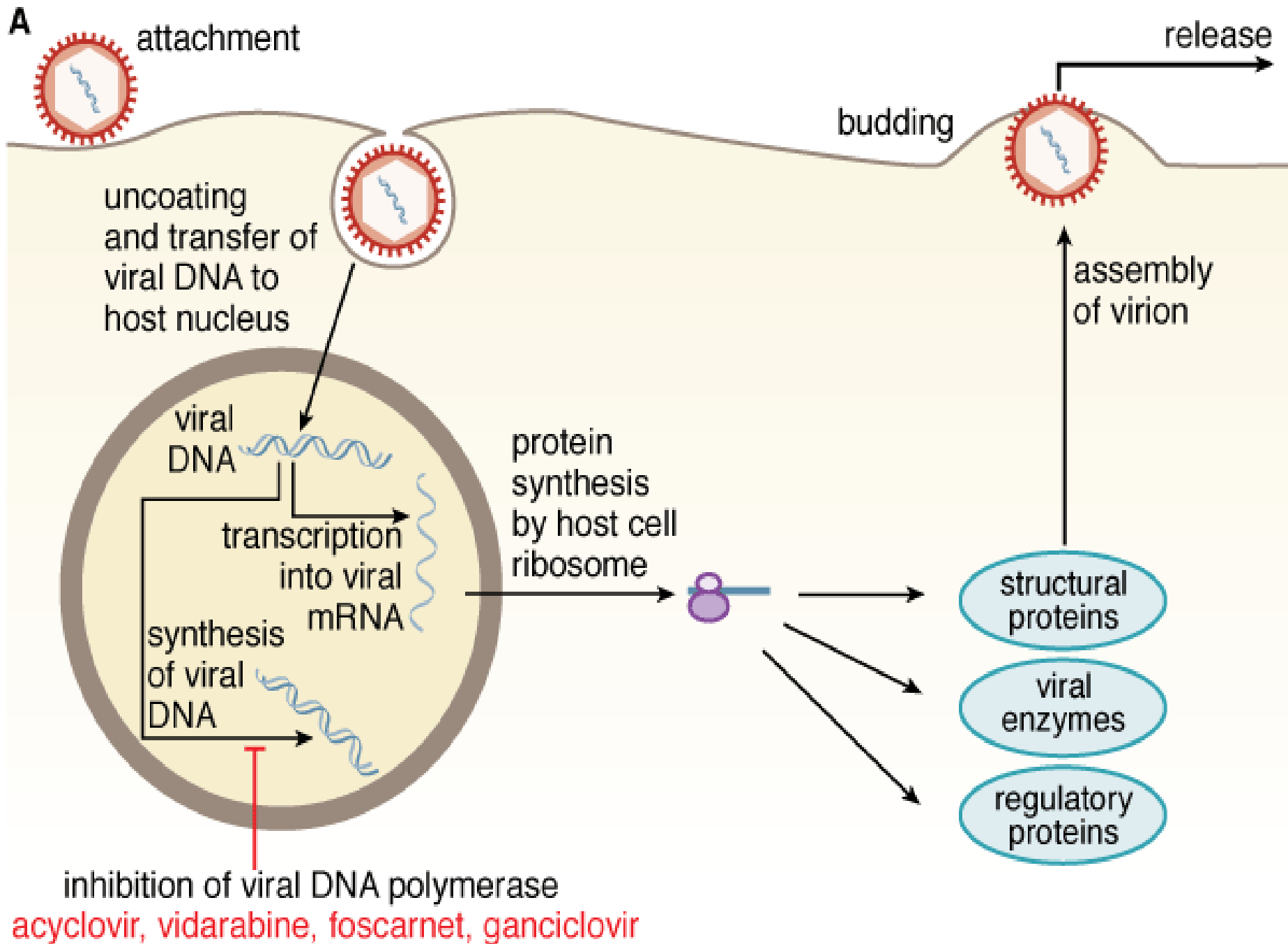
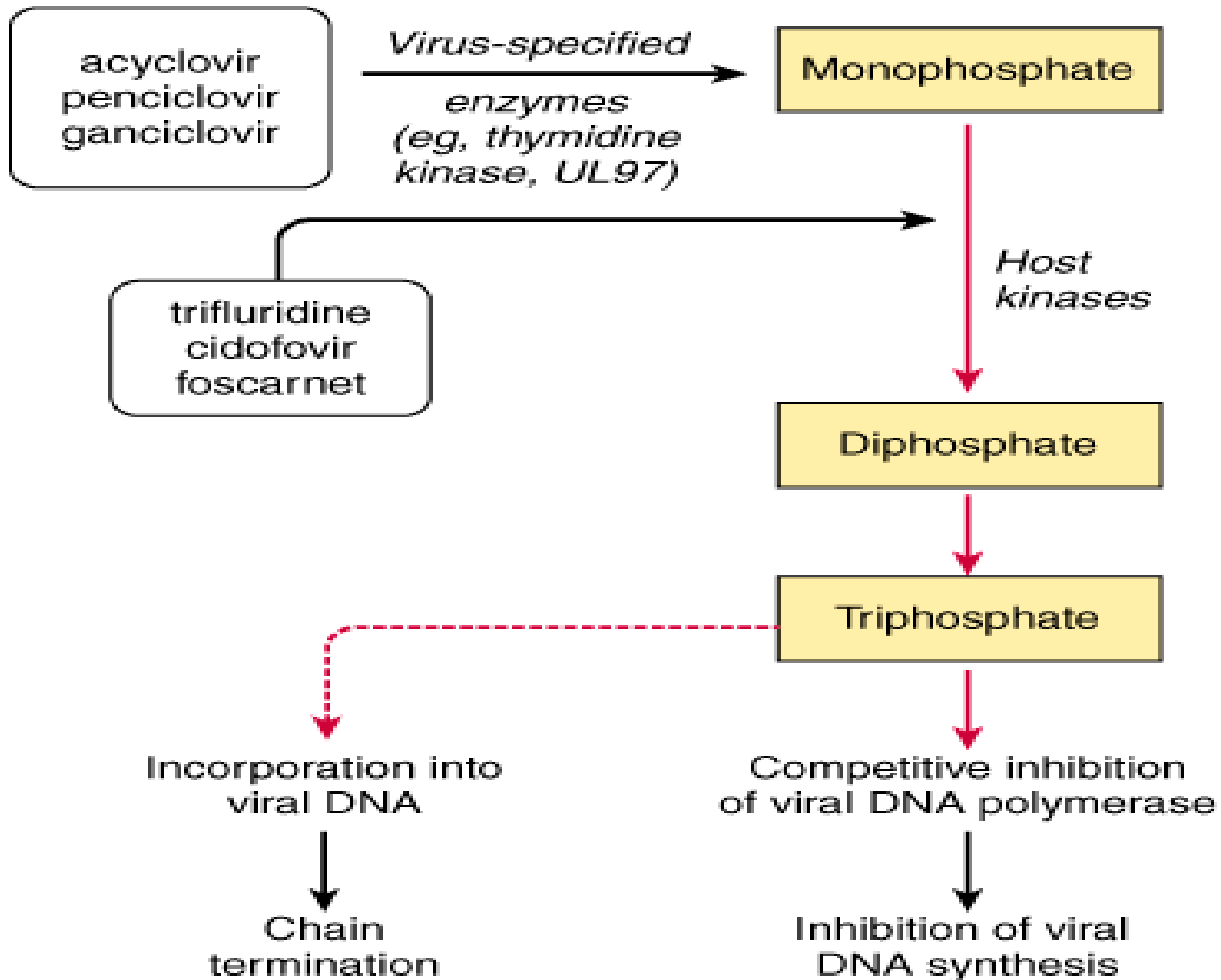


# ANTIHERPES VIRUS AGENTS

- Acyclovir and Valacyclovir
  - Penciclovir and Famciclovir
  - Ganciclovir and Valganciclovir
  - Cidofovir (**Cytosine**)
  - Foscarnet (**Inorganic pyrophosphate**)
  - Fomivirsen (**Antisense oligonucleotide**)
  - Docosanol (**long chain saturated alcohol**)
  - Idoxuridine, Trifluridine (**Thymidine**)
- } (**Guanine**)

Herpes simplex virus 1(HSV1), Herpes simplex virus 2(HSV2), Varicella zoster virus(VZV), Epstein barr virus(EBV), Cytomegalo virus(CMV)





**Acyclovir : IV, oral, topical ophthalmic**

**Mycophenolate mofetil** depletes intracellular dGTP pools so potentiates acyclovir.

## **Therapeutic uses**

**Oral** --- First episode and recurrent genital herpes, Genital herpes suppression, Herpes proctitis, Orolabial herpes, Orolabial herpes suppression, Mucocutaneous herpes in immuno-compromised host, Varicella zoster. Prophylactically in organ transplant patients



### Herpes Blisters



Early Stage



Later Stage



## **I.V. Acyclovir**

Severe HSV treatment, Mucocutaneous herpes in the immunocompromised host, Herpes encephalitis, Neonatal herpes simplex virus infection, Varicella or zoster in immunocompromised host

Prophylactically in organ transplant patients

## **Topical Acyclovir**

Herpes labialis, Recurrent herpes labialis  
Herpetic keratoconjunctivitis

**CMV prophylaxis** in immunocompromised patients

**Oral acyclovir plus systemic corticosteroids** tried in bell's palsy

### **Adverse effects**

Well tolerated. Nausea, diarrhea, and headache.

Intravenous infusion: **reversible renal and neurologic toxicity.**

High doses --- **chromosomal damage** and **testicular atrophy in rats**, no evidence of teratogenicity, reduction in sperm production.

# **Famciclovir, Penciclovir**

## **Oral**

First episode genital herpes, Recurrent genital herpes, Genital herpes suppression, Orolabial herpes, Orolabial or genital herpes suppression, Orolabial or genital herpes in immuno-suppressed host, Herpes zoster.

## **Alternative to Acyclovir.**

Thymidine kinase - deficient, acyclovir resistant herpes viruses are cross-resistant to famciclovir and penciclovir.



## **Idoxuridine : Topical, Ophthalmic**

HSV keratitis --- more effective in epithelial infections than in stromal infections.

## **Trifluridine : Topical, Ophthalmic**

Keratoconjunctivitis and recurrent epithelial keratitis.

Cutaneous application alone or combination with interferon alfa successful in acyclovir-resistant HSV infections

**Common adverse reactions** --- pain, edema of lids, pruritus and inflammation; allergies.

## **Docosanol --- topical skin**

- Inhibits fusion between plasma membrane and HSV envelope. Application site reactions occur. Recurrent orolabial herpes.

## **Ganciclovir: IV, Oral, Intravitreal, Ophthalmic gel, Sustained release intra-ocular implant**

Active against CMV, HSV, VZV, EBV, HHV-6, and HHV-8.

- Delays progression of CMV retinitis in AIDS.
- Dual therapy with foscarnet more effective.

## **I.V. Ganciclovir**

- CMV colitis, esophagitis, pneumonitis (ganciclovir plus CMV immunoglobulin) in immunocompromised patients.
- Reduces CMV infection in transplant patients. Risk of Kaposi's sarcoma reduced.

**Oral** --- Poor bioavailability

**Ophthalmic gel** --- HSV keratitis

**Intraocular** --- CMV retinitis --- direct intravitreal injection or intraocular implant.

## **Adverse effects**

- **Myelosuppression.**

- Severe GIT disturbances, fever, rash, headache, insomnia, peripheral neuropathy.
- CNS Toxicity and hepatotoxicity rare.
- Teratogenicity in animals.

**Zidovudine / azathioprine /  
mycophenolate mofetil + Ganciclovir ---  
Increased Myelosuppression**

- Intravitreal ganciclovir --- vitreous hemorrhage and retinal detachment.

## **Foscarnet : IV, Intravitreal injections**

Acyclovir-resistant HSV and VZV infection  
Ganciclovir-resistant CMV retinitis, other CMV infections.

Reduces the risk of Kaposi's sarcoma.

**Adverse effects:** renal impairment, hypo or hyper calcemia, hypo or hyper phosphatemia, hypokalemia and hypomagnesemia. Nausea, vomiting, anemia, elevated liver enzymes. CNS toxicities.

**Safety in pregnancy/childhood uncertain**

## **CIDOFOVIR (topical, i.v.)**

Active against CMV, HSV-1, HSV-2, VZV, EBV, HHV-6, HHV-8, adenovirus, poxviruses, polyomaviruses, and human papillomavirus.

**i.v. Cidofovir** - CMV retinitis, adenovirus, human papillomavirus, vaccinia and poxvirus infections.

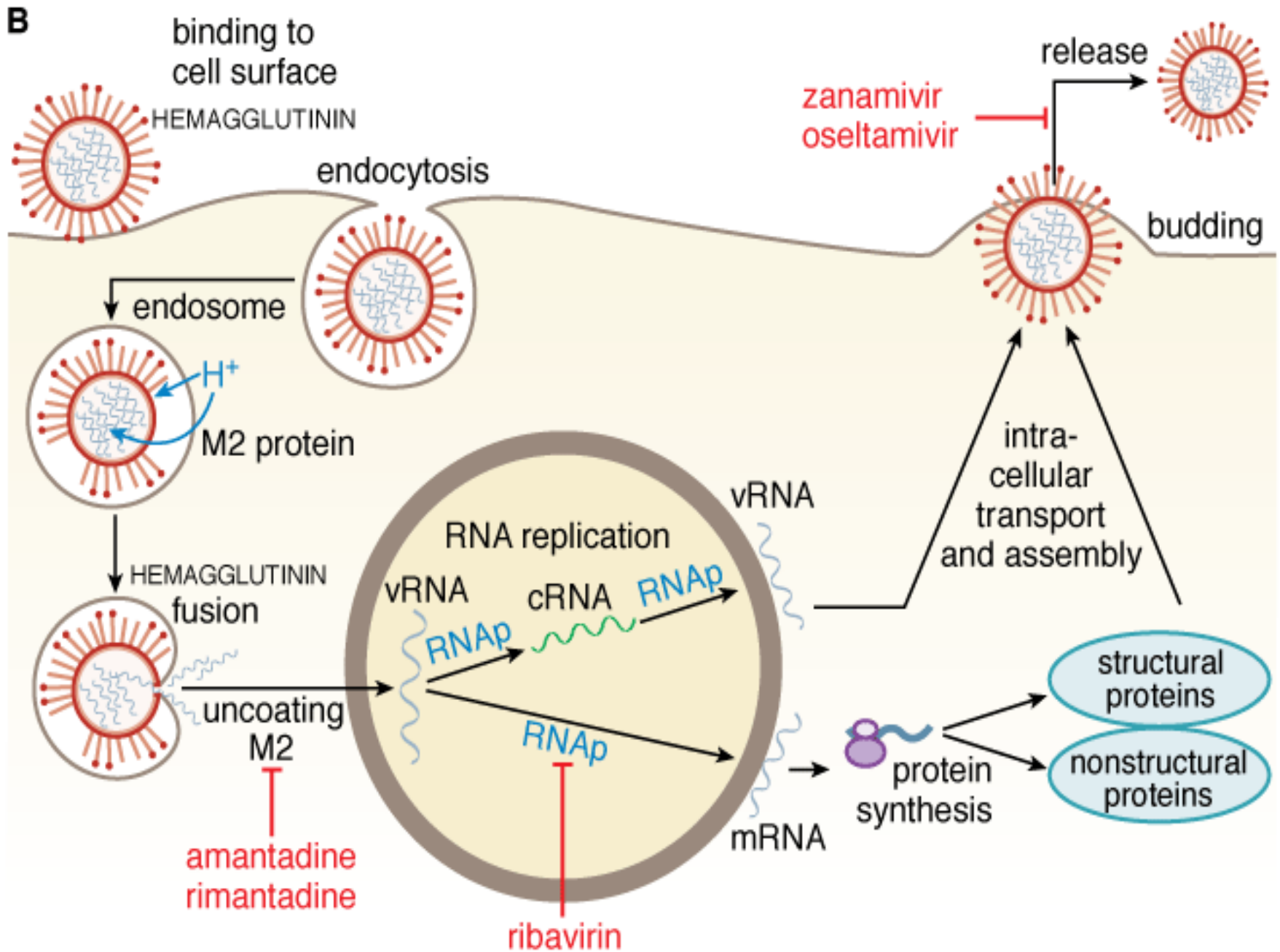
**Adverse effects** - proximal tubular nephrotoxicity. Proteinuria, metabolic acidosis, Fanconi's syndrome, uveitis, ocular hypotony, and neutropenia (15– 24%).

## **Fomivirsen** : Intravitreal injection

- First FDA approved **Antisense oligonucleotide** directed against CMV mRNA.
- For **CMV retinitis** when resistance to ganciclovir, foscarnet, cidofovir. HIV patients with refractory, sight-threatening CMV retinitis.
- Significant delay in progression.

## **Ocular side effects** :

Iritis ( topical corticosteroids); vitritis; cataracts and increased IOP.





# **Anti-influenza agents**

## **Amantadine, Rimantadine : Oral**

Inhibit viral uncoating; in some may affect a late step in viral assembly. Influenza B not affected.

Both rarely used now due to emergence of resistance. Amantadine rarely for Parkinsonism.

**Adverse effects** : Well tolerated , minor GI and CNS toxicity

**Oseltamivir** :: Oral, **Zanamivir** :: Inhaled  
**Peramivir**:: Single dose i.v.

- Treatment / prevention of influenza A and B.
- Reduces illness duration, speeds recovery and **reduces risk of complications and transmission.**
- Prophylaxis of unimmunized working adults and immunized nursing home residents.

**Adverse effects: Oral** --- nausea, abdominal discomfort, emesis, owing to local irritation.

**Inhalation** --- cough, bronchospasm, reversible decrease in pulmonary function, and transient nasal and throat discomfort.

# Antihepatitis B Agents

**Adefovir dipivoxil: Oral** :: 10mg/day

HBV, HSV and HIV virus.

Active against lamivudine-resistant HBV.

**Adverse effects** --- Dose-related

**nephrotoxicity and tubular dysfunction** -

-- hypophosphatemia, acidosis, glycosuria and proteinuria.

Increased risk of lactic acidosis with antiretroviral agents.

**Lamivudine** --- (Cytosine analogue)– No longer first line for HBV

**Tenofovir disoproxil fumarate** (First line now)--- Adenosine analog (nucleotide)

**Telbivudine** --- ( Thymidine analogue)

**Entecavir** --- (Guanosine Analogue) most active First line for HBV, weak anti HIV activity. For Lamivudine resistant cases.

**Adefovir dipivoxil** --- Least active against HBV not first line.

**Ribavirin : Oral, i.v., Aerosol :**

**Broadspectrum:**

- **HCV/HIV** coinfecting patients.
- Recurrent HCV infection after liver transplantation.

I.V. and/or aerosol ribavirin

- **RSV** bronchiolitis and pneumonia in hospitalized children and severe **influenza virus (A and B)**.

- Immunosuppressed patients with **adenovirus, vaccinia, parainfluenza** or **measles**.

- Resistance rare

## **Adverse effects**

**Aerosol** : conjunctival irritation, rash, transient wheezing.

**Systemic**: dose-related reversible anemia. Bone marrow depression, CNS and GI symptoms.

Teratogenic effects

**Contraindicated in pregnancy**, end stage renal failure, ischaemic valvular disease, anemia.

**Interferon Alfa** : intralesional, i.v., i.m., s.c.  
Low molecular wt glycoprotein cytokines.  
**Antiviral, immunomodulating, anti-proliferative action.**

Inhibit viral penetration, translation, protein processing, transcription, maturation, increase in major histocompatibility complex antigens, enhanced phagocytosis by macro-phages, increased survival of CT4 cells.

Two pegylated IFNs alfa-2a and alfa-2b available commercially.

## **Adverse effects**

- Acute influenza like syndrome
- Dose-limiting --- **Myelosuppression** --- granulocytopenia and thrombocytopenia
- **Neurotoxicity** : somnolence, confusion, behavioral disturbance, rarely seizures
- Thyroiditis, cardiotoxicity, elevated triglycerides, alopecia, proteinuria, hepatotoxicity.

## **Contraindications:**

- hepatic decompensation, autoimmune disease, history of cardiac arrhythmia and pregnancy



## **New Direct acting Anti HCV drugs**

- Used in combination among themselves or with Ribavirin ± PegINFα
- Achieve upto 99% SVR and shorten duration of therapy to 12-14 weeks
- Much less toxic than Ribavirin and PegINFα

## **NS5B Polymerase Inhibitor: Sofosbuvir**

- Uridine analogue Prodrug--- triphosphate inhibits HCV RNA polymerase.
- substrate for Pgp efflux transporter
- **ADR:** Abdominal pain, fatigue, agitation, joint pain anemia.

## **NS3/4A Protease inhibitor: Simeprevir**

- Inhibits HCV protease which blocks cleavage of HCV polyprotein complex.
- Substrate for CYP3A4, Pgp Efflux transporter

**ADR:** Nausea, headache, dyspnoea, fatigue, rash and phototoxicity.

## **NS5A inhibitors:**

NS5A Multifunctional protein involved in replication of HCV and assembly of progeny virions.

**Daclatasvir, Ledipasvir, Velpatasvir**