Anti-viral Drugs

Anti-viral drugs

- Viruses have no cell wall and made up of nucleic acid components
- Viruses containing envelope – antigenic in nature
- Viruses are obligate intracellular parasite
- They do not have a metabolic machinery of their own – use host enzymes

Anti-viral drugs

- Certain viruses multiply in the cytoplasm but others do in the nucleus
- Most multiplication take place before diagnosis is made

Anti-Viral drugs

- Many antiviral drugs are *Purine* (A & G) or *Pyrimidine* (C & T) analogs.
- Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active.
- Anti-viral agents inhibits active replication so the viral growth resumes after drug removal.

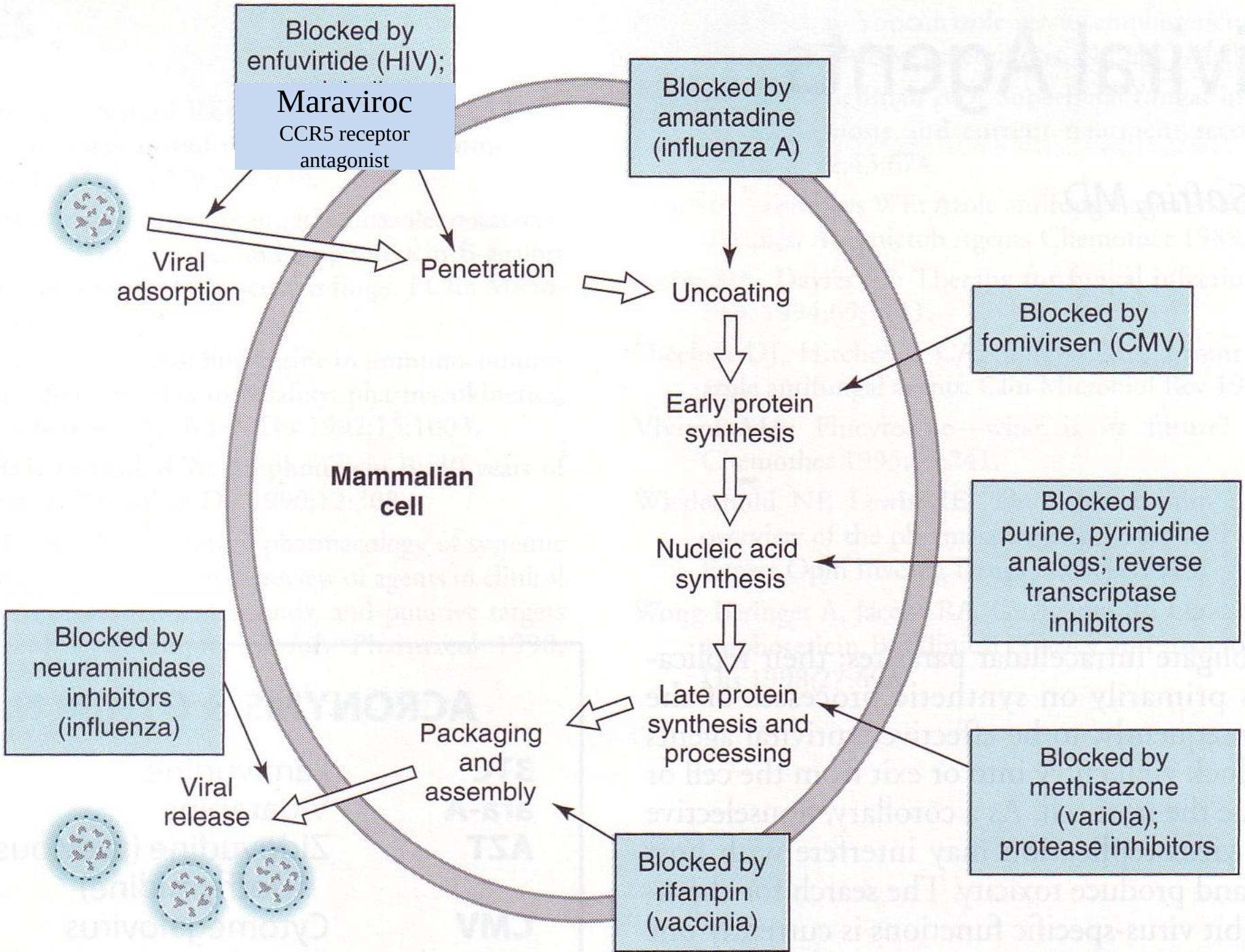
Anti-viral drugs

- Current anti-viral agents do not eliminate non-replicating or latent virus
- Effective host immune response remains essential for the recovery from the viral infection
- Clinical efficacy depends on achieving inhibitory conc. at the site of infection within the infected cells

Anti-viral drugs

Stages of viral replication

- Cell entry – Attachment
  - Penetration
- Uncoating
- Transcription of viral genome
- Translation
- Assembly of virion components
- Release


Blocked by enfuvirtide (HIV);
Maraviroc
CCR5 receptor antagonist
Blocked by amantadine (influenza A)
Viral adsorption
Penetration
Uncoating
Blocked by fomivirsen (CMV)
Early protein synthesis
Mammalian cell
Nucleic acid synthesis
Blocked by purine, pyrimidine analogs; reverse transcriptase inhibitors
Blocked by neuraminidase inhibitors (influenza)
Late protein synthesis and processing
Packaging and assembly
Viral release
Blocked by methisazone (variola); protease inhibitors
Blocked by rifampin (vaccinia)

Anti-viral drugs

Anti-herpes virus agents

- Acyclovir / Valacyclovir
- Famciclovir / Penciclovir
- Ganciclovir / Cidofovir
- Foscarnet
- Trifluridine / Idoxuridine / Vidarabine

Anti-viral drugs

Acyclovir & related compounds:

- Valacyclovir is a prodrug of Acyclovir with better bioavailability.
- Famciclovir is hydrolyzed to Penciclovir and has greatest bioavailability.
- Penciclovir is used only topically whereas Famciclovir can be administered orally.

Anti-Viral drugs

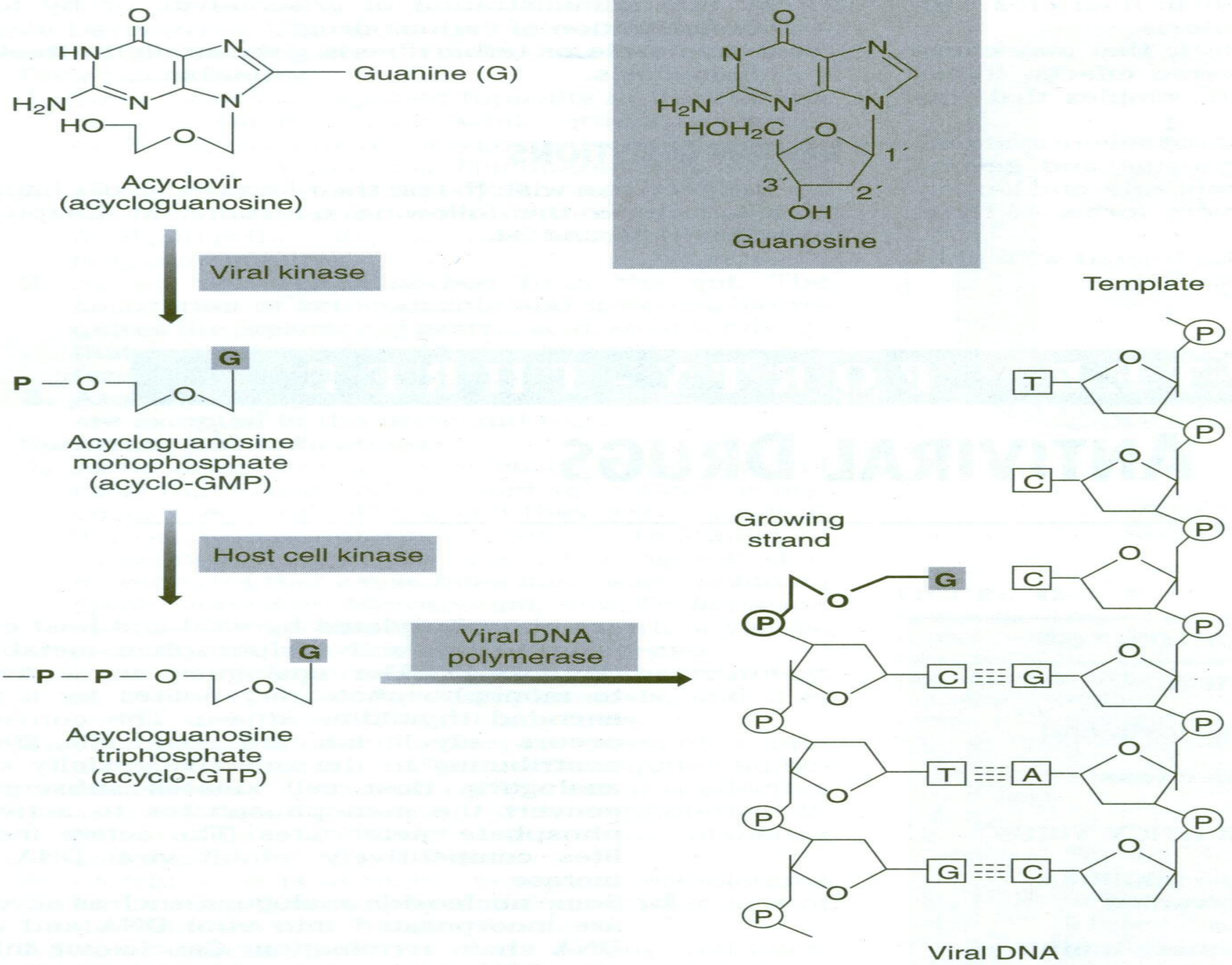
Pharmacology of acyclovir and related compounds

- Acyclovir, Valacyclovir, Ganciclovir, Famciclovir, Penciclovir all are guanine nucleoside analogs.

Anti-viral drugs

Mechanism of action of Acyclovir and related compounds :

- All drugs are phosphorylated by a viral thymidine-kinase, then metabolized by host cell kinases to nucleotide analogs.
- The analog inhibits viral DNA-polymerase
- Incorporation of acyclovir triphosphate into the growing viral DNA chain
- Only actively replicating viruses are inhibited


Guanine (G)
Acyclovir
(acycloguanosine)
Guanosine
Viral kinase
Acycloguanosine
monophosphate
(acyclo-GMP)
Host cell kinase
Acycloguanosine
triphosphate
(acyclo-GTP)
Viral DNA
polymerase
Template
Growing
strand
Viral DNA

Anti-viral drugs

- Acyclovir is thus selectively activated in cells infected with herpes virus.
- Uninfected cells do not phosphorylate acyclovir.

Anti-Viral drugs

Antiviral spectrum :

- Acyclovir: HSV-1, HSV-2, VZV, Shingles.
- Ganciclovir / Cidofovir : CMV
- Famciclovir : Herpes genitalis and shingles
- Foscarnet : HSV, VZV, CMV, HIV
- Penciclovir : Herpes labialis
- Trifluridine : Herpetic keratoconjunctivitis

Anti-Viral drugs

Pharmacokinetics of Acyclovir :

- Oral bioavailability ~ 20-30%
- Distribution in all body tissues including CNS
- Renal excretion: > 80%
- Half lives: 2-5 hours
- Administration: Topical, Oral , IV

Anti-viral drugs

Adverse effects of Acyclovir / Ganciclovir

- Nausea, vomiting and diarrhea
- Nephrotoxicity - crystalluria, haematuria, renal insufficiency
- Myelosuppression – Neutropenia and thrombocytopenia – Ganciclovir

Anti-viral drugs

Therapeutic uses :

Acyclovir* is the drug of choice for*:

- HSV Genital infections
- HSV encephalitis
- HSV infections in immunocompromised patient

Ganciclovir* is the drug of choice for*:

- CMV retinitis in immunocompromised patient
- Prevention of CMV disease in transplant patients

Anti-viral drugs

Cidofovir :

- It is approved for the treatment of CMV retinitis in immunocompromised patients and Adenovirus infections
- It is a nucleotide analog of cytosine – no phosphorylation required.
- It inhibits viral DNA synthesis
- Available for IV, Intravitreal inj, topical
- Nephrotoxicity is a major disadvantage.

Anti-viral drugs

PHARMACOLOGY OF VIDARABINE

- Vidarabine is a nucleoside analog. (adenosine)

Antiviral spectrum of Vidarabine :

HSV-1, HSV-2 and VZV.

Its use is limited to HSV keratitis only

Anti-viral drugs

Vidarabine

- The drug is converted to its triphosphate analog which inhibits viral DNA-polymerase.
- Oral bioavailability ~ 2%
- Administration: Ophthalmic ointment
- Used in HSV keratoconjunctivitis in immunocompromised patient.
- Anemia and SIADH are adverse effects.

Anti-viral drugs

PHARMACOLOGY OF TRIFLURIDINE

- Trifluridine is a Pyrimidine nucleoside analogs - inhibits viral DNA synthesis.

Antiviral spectrum Trifluridine :

- HSV-1, HSV-2 and VZV.
- Use is limited to Topical - Ocular HSV Keratitis

Anti-viral drugs

PHARMACOLOGY OF FOSCARNET

- Foscarnet is an inorganic pyrophosphate analog
- It directly inhibits viral DNA and RNA - polymerase and viral reverse transcriptase (it does not require phosphorylation for antiviral activity)

Anti-viral drugs

Foscarnet

- HSV-1, HSV-2, VZV, CMV and HIV.
- Oral bioavailability ~ 10-20%
- Distribution to all tissues including CNS
- Administration: IV

Anti-viral drugs

Therapeutic uses of Foscarnet

- ***It is an alternative drug for***
- HSV infections (acyclovir resistant / immunocompromised patient)
- CMV retinitis (ganciclovir resistant / immunocompromised patient)

Anti-viral drugs

Respiratory viral infections

Influenza –

- Amantadine / Rimantadine
- Oseltamivir / Zanamavir
  (Neuraminidase inhibitors)

RSV bronchiolitis –

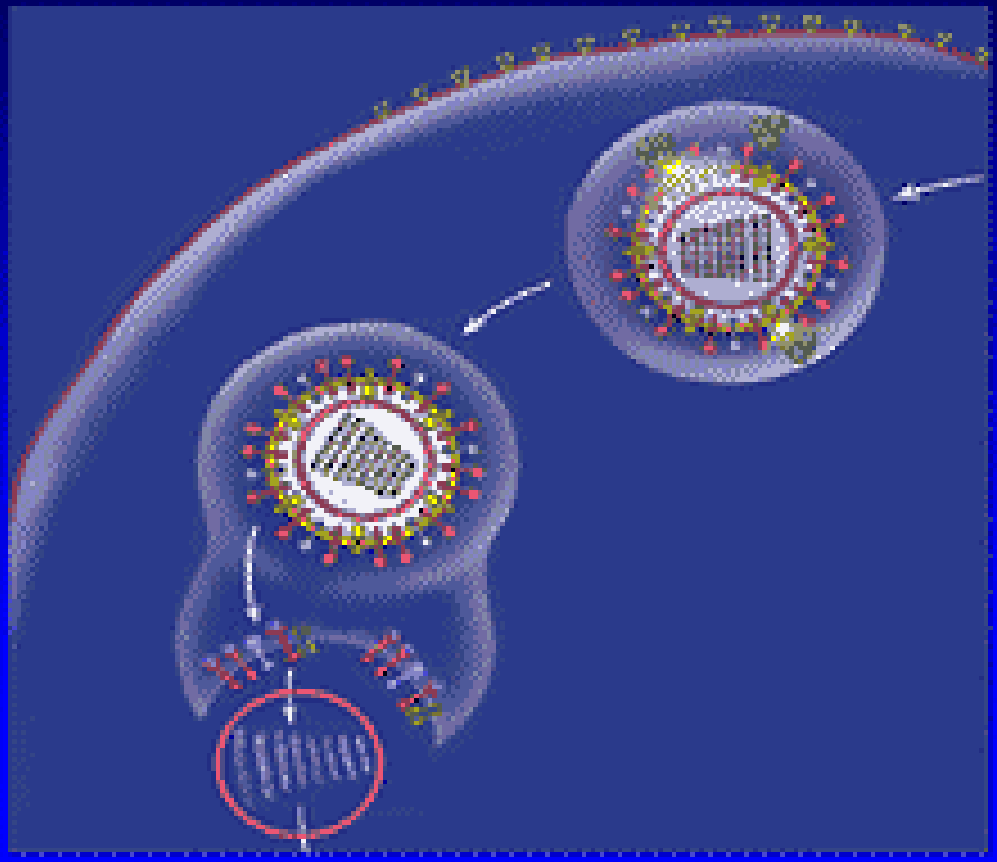
- Ribavirin

Anti-viral drugs

Amantadine and Rimantadine : Influenza

- Prevention & Treatment of influenza A
- **Inhibition of viral uncoating** by inhibiting the viral membrane protein M2
- Influenza A virus only

Amantadine and Rimantadine: Mechanism of Action



- Blocks M2 protein channel (type A only)
- Disrupts hydrogen transport, viral uncoating in host cell and therefore viral RNA transcription

Anti-viral drugs

Pharmacokinetics of Amantadine

- Oral bioavailability ~ 50-90%
- Amantadine cross extensively BBB whereas Rimantadine does not cross extensively .
- Administration: Oral

Anti-viral drugs

Neuraminidase inhibitors : Influenza A & B
Oseltamivir / Zanamavir

- **Influenza** contains an enzyme *neuraminidase* which is essential for the replication of the virus.
- ***Neuraminidase inhibitors*** prevent the release of new virions and their spread from cell to cell.

Anti-viral drugs

Neuraminidase inhibitors : Influenza
Oseltamivir / Zanamavir

- These are effective against both types of influenza A and B.
- Do not interfere with immune response to influenza A vaccine.
- Can be used for both prophylaxis and acute treatment.

Anti-viral drugs

Neuraminidase inhibitors : Influenza

Oseltamivir / Zanamavir

- Oseltamivir is orally administered.
- Zanamavir is given intranasal.
- Risk of bronchospasm with zanamavir

Anti-viral drugs

PHARMACOLOGY OF RIBAVIRIN

- **Ribavirin** is a guanosine analog.
- Requires phosphorylation to mono-, di- and triphosphate
- Triphosphate Inhibits RNA polymerase and depletes cellular stores of guanine (inhibit IMDH)
- Decrease synthesis of mRNA 5’ cap (interfere with guanylation and methylation of nucleic acid base)

Antiviral spectrum : RNA viruses are susceptible, including influenza, parainfluenza viruses, **RSV,** Lassa virus

Anti-viral drugs

Ribavirin : RSV

- Distribution in all body tissues, except CNS
- Administration : Oral, IV, Inhalational in RSV.
- Anemia and jaundice are adverse effects
- Not advised in pregnancy.

Anti-viral drugs

Therapeutic uses Ribavirin

Ribavirin is the drug of choice for:

- RSV bronchiolitis and pneumonia in hospitalized children (given by aerosol)
- Lassa fever

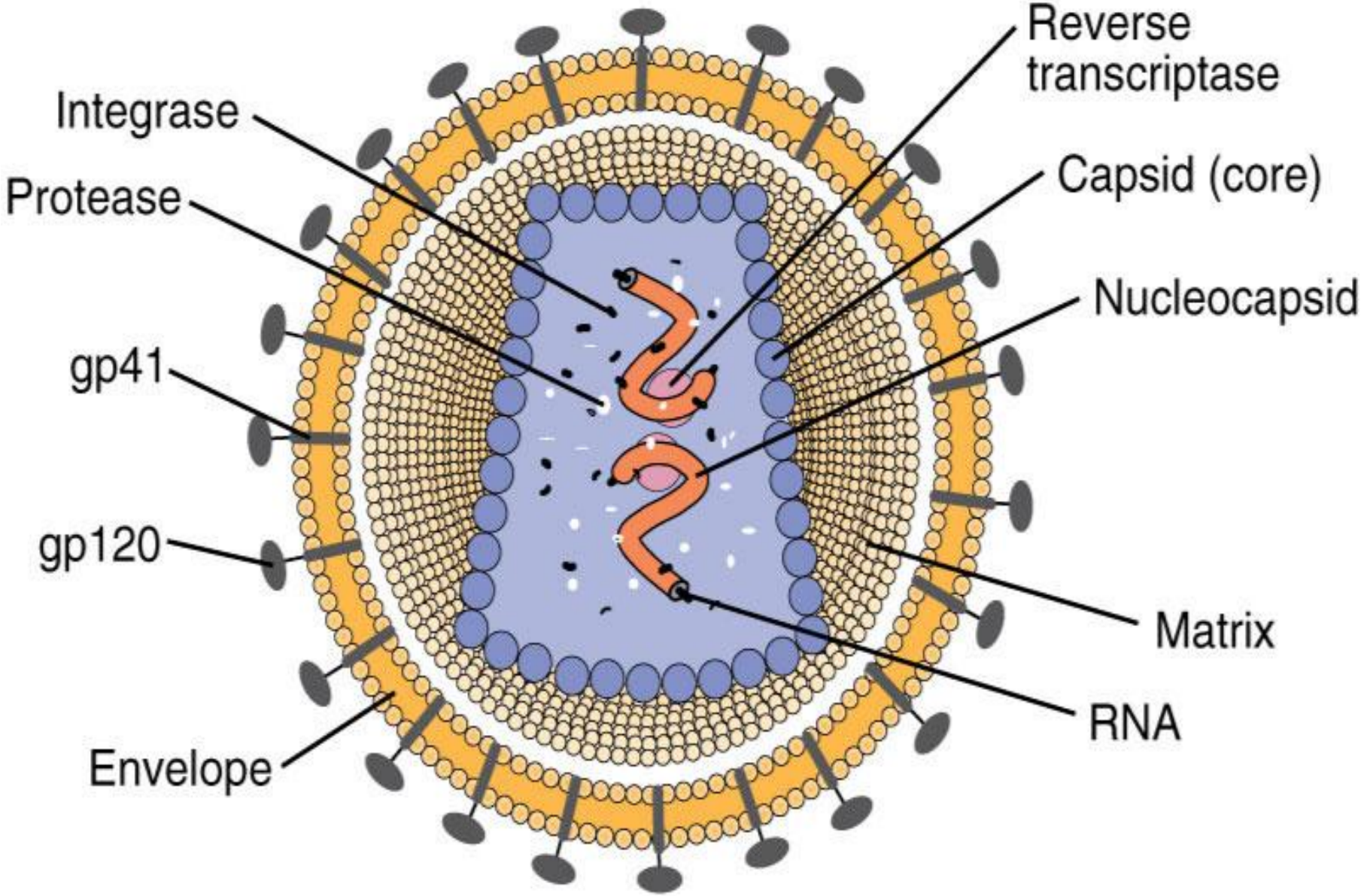
Ribavirin is an alternative drug for:

- Influenza, parainfluenza, measles virus infection in immunocompromised patients

Anti-viral drugs

Hepatic Viral infections :

- Interferons
- Lamivudine – cytosine analog – HBV
- Entecavir – guanosine analog – HBV – lamivudine resistance strains
- Ribavirin – Hepatitis C (with interferons)
- Sofosbuvir - nucleotide analog used in combination with other drugs (Ribavirin and Interferon) for the treatment of hepatitis C virus (HCV) infection. Course of 12 weeks cost 84,000$.



(From Dorland's illustrated medical dictionary, *ed 30, Philadelphia, 2003, Saunders.)*

Fig. 39-2. Human immunodeficiency virus (HIV). Within the core capsid, the diploid, single-stranded, positive-sense RNA is complexed to nucleoprotein.

Antiretroviral Drugs

<u>HAART - Highly active antiretroviral therapy</u>

- Includes **at least three medications**
  - "cocktails"

- These **medications work in different ways to reduce the viral load**

Antiretroviral Drugs

- **Fusion inhibitors**
  - Inhibit viral fusion, preventing viral replication
  - Newest class of antiretroviral drugs
  - Example: enfuvirtide (Fuzeon)
  - Used in combination with other drugs active against HIV
  - Side effects:
    - peripheral neuropathy, insomnia, depression, cough, dyspnoea, anorexia, arthralgia

Antiretroviral Drugs

- **Entry inhibitor**
  - Inhibit viral entry into macrophages a T-cells
  - CCR5 receptor antagonist
  - FDA approved in 2007
  - Maraviroc (**Selzentry**, or **Celsentri** outside the U.S)
  - Used in combination with other drugs active against HIV
  - HIV can also use other coreceptors, such as CXCR4, an HIV tropism test such as a trofile assay must be performed to determine if the drug will be effective
  - Safety issues regarding blocking CCR5, a receptor whose function in the healthy individual is not fully understood

Antiretroviral Drugs

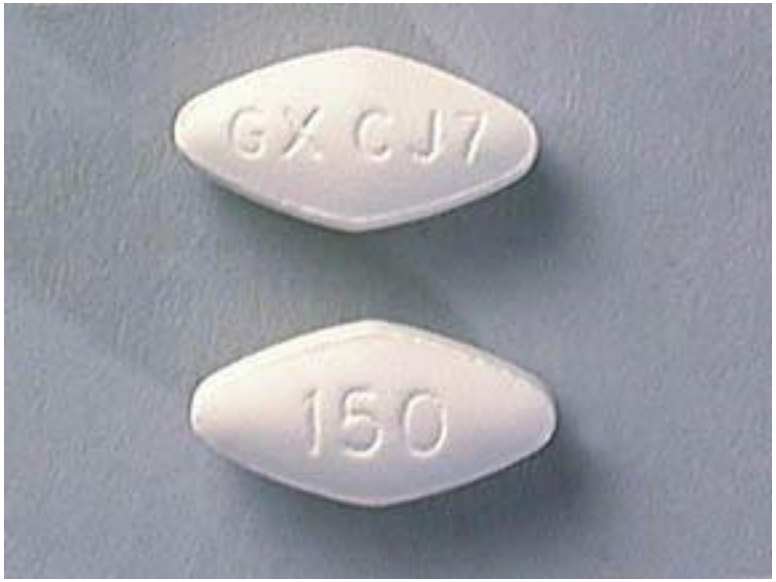
- **Reverse transcriptase inhibitors (RTIs)**
  - Block activity of the enzyme reverse transcriptase, preventing production of new viral DNA
- **Reverse transcriptase inhibitors (RTIs)**
  - Nucleoside RTIs (NRTIs): Azidothymidine (AZT), Didanosine (ddI), Stavudine (D4T), Lamivudine (3TC)
  - Nonnucleoside RTIs (NNRTIs): Nevirapine, delavirdine, efavirenz
  - Nucleotide RTIs (NTRTIs):Tenofovir, Adefovir

Nucleoside RTIs (NRTIs):

Azidothymidine (AZT), Didanosine (ddI), Stavudine (D4T), Lamivudine (3TC)

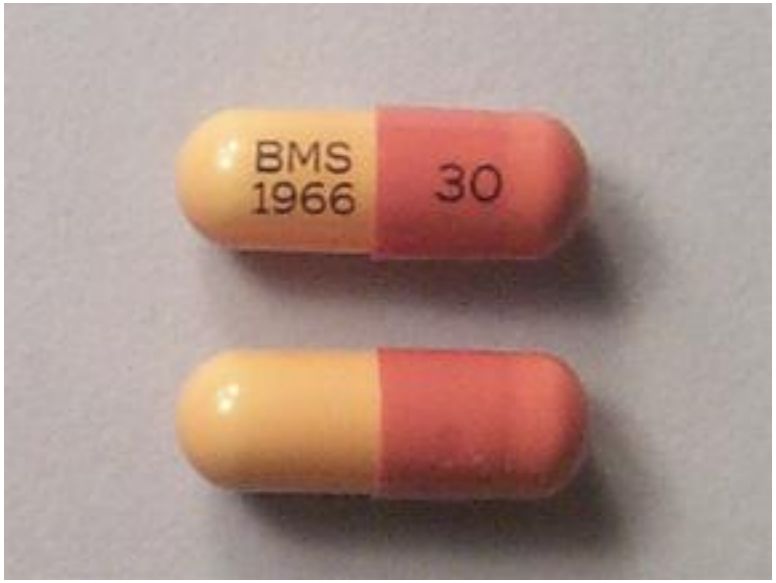
- Requires phosphorylation by host cellular enzymes (kinases) to their active triphosphate form
- Selective theraputic effect: HIV RT is more sensitive to AZT than is host cell DNA polymerase

3TC (lamivudine/Epivir)



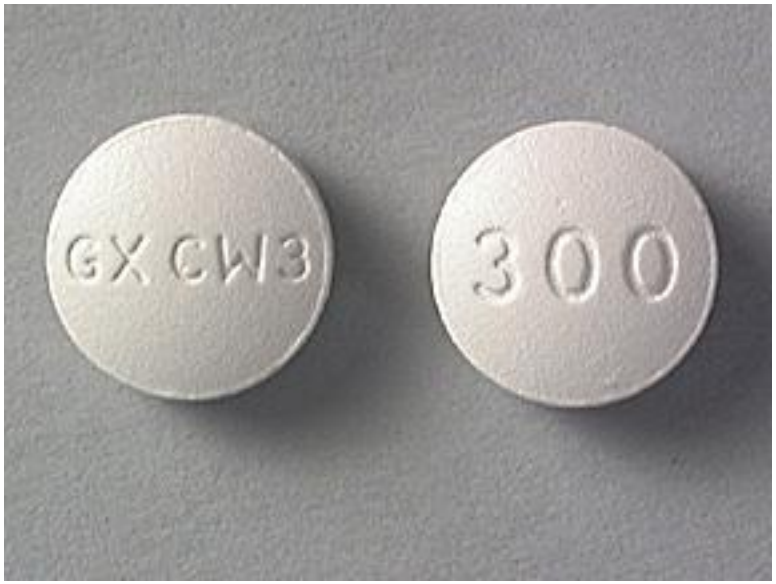
- **Toxicity**
  - Few
  - Hepatitis B exacerbation
- **Side Effects**
  - Few; class effect
- **Dosing**
  - 150mg bid or
  - 300mg qd
  - Renal dosing available
- **Special Considerations**
  - Hepatitis B
- **Combination with AZT**

D4T (stavudine/Zerit)



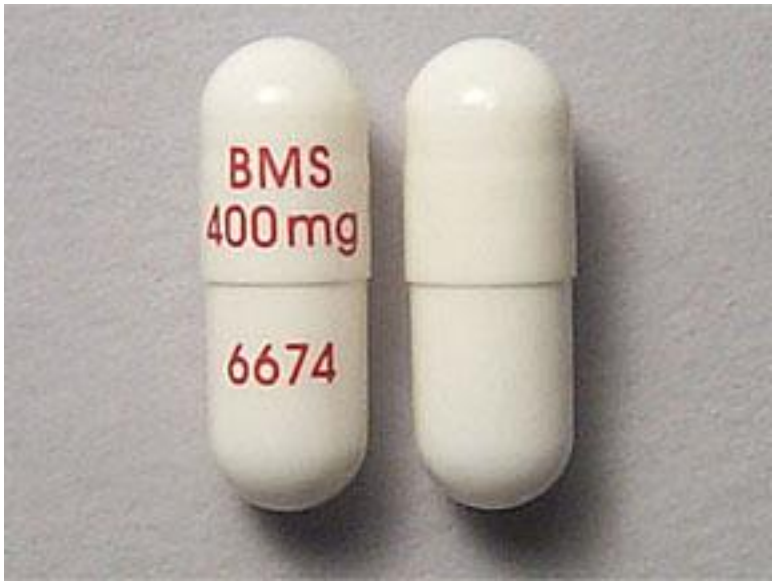
- **Toxicity**
  - Lipoatrophy
  - Peripheral neuropathy
  - Pancreatitis
  - Lactic acidosis
- **Side Effects**
  - Gen well-tolerated
  - H/N/V
- **Dosing**
  - 40mg bid (if >60kg)
  - 30mg bid (if <60kg)
- **Combination only**

AZT (zidovudine/Retrovir)



- **Toxicity**
  - Anemia
  - Neutropenia
  - Thrombocytopenia
  - Myopathy
- **Side Effects**
  - Nausea/vomiting
  - Headache
  - Dizziness
- **Dosing**
  - 300mg bid
- **Combination only**

DDI (didanosine/Videx)



- **Toxicity**
  - Lactic acidosis
  - Peripheral neuropathy
  - Pancreatitis
  - Lipodystrophy
- **Side Effects**
  - GI
- **Dosing**
  - If EC, 400mg QD (<60kg: 250mg qd)
  - If reg tabs, 200mg bid (<60kg:125 bid/250qd)
  - Empty stomach
- **Combination only**

Nonnucleoside RTIs (NNRTIs):
Nevirapine, delavirdine, efavirenz

- Active against HIV-1
- Do not require cellular enzymes to be phosphorylated
- Do not inhibit human DNA polymerase
- Relatively safe: noncytotoxic
- Highly prone to drug resistance
- Used in combination with other drugs active against HIV

Integrase enzyme inhibitors

A class of antiretroviral drug designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell

- Raltegravir
- Elvitegravir
- Dolutegravir

- MK-2048

Antiretroviral Drugs

- **Protease inhibitors (PIs)**
  - Inhibit the protease retroviral enzyme, preventing viral replication
  - Inhibition of this enzyme blocks viral assembly and release
  - **Examples:**

    amprenavir (Agenerase)
    indinavir (Crixivan)
    nelfinavir (Viracept)
    ritonavir (Norvir)
    saquinavir (Invirase)
  - Hepatotoxic
  - Used in combination with other drugs active against HIV

Antiretroviral Drugs

- **Combinations of multiple antiretroviral medications** are common
- **Adverse effects vary with each drug** and may be severe–**monitor for dose-limiting toxicities**
- Monitor for **signs of opportunistic diseases**

Anti-viral drugs

Interferons

Interferons (IFNs) are natural proteins produced by the cells of the immune systems in response to challenges by foreign agents such as viruses, bacteria, parasites and tumor cells.

- Antiviral, immune modulating and anti-proliferative actions
- Three classes of interferons – **α , β, γ**

Anti-viral drugs

Interferons

- **α and β interferons** are produced by all the cells in response to *viral infections*
- **γ interferons** are produced only by T lymphocyte and NK cells in response to cytokines – *immune regulating effects*
- γ has less anti-viral activity compared to α and β interferons

Anti-viral drugs

Mechanism of action of Interferons :

- **Induction** of the following enzymes:

1) a protein kinase which inhibits protein synthesis

2) an oligo-adenylate synthase which leads to degradation of viral mRNA

3) a phosphodiesterase which inhibit t-RNA

The action of these enzymes leads to an **inhibition of translation**

Anti-viral drugs

Antiviral spectrum : Interferon α

- Includes HBV, HCV (Pegylated interferon) and HPV.
- addition of polyethylene glycol to the interferon, through a process known as pegylation, enhances the half-life of the interferon when compared to its native form
- Anti-proliferative actions may inhibit the growth of certain cancers - like Kaposi sarcoma and hairy cell leukemia.

Anti-viral drugs

Pharmacokinetics : Interferons

- Oral bioavailability: < 1%
- Administered Intralesionally, S.C, and I.V
- Distribution in all body tissues, except CNS and eye.
- Half lives: 1-4 hours

Anti-viral drugs

Adverse effects of Interferons

- Acute flu-like syndrome (fever, headache)
- Bone marrow suppression (granulocytopenia, thrombocytopenia)
- Neurotoxicity (confusion, seizures)
- Cardiotoxicity - arrhythmia
- Impairment of fertility

Anti-viral drugs

Therapeutic uses Interferons

- Chronic hepatitis B and C (complete disappearance is seen in 30%).
- HZV infection in cancer patients (to prevent the dissemination of the infection)
- CMV infections in renal transplant patients
- Condylomata acuminata (given by intralesional injection). Complete clearance is seen ~ 50%.
- Hairy cell leukemia (in combination with zidovudine)
- AIDS related Kaposi's sarcoma

Virus	Diseases	Drug(s) of choice	Alternative drugs
FLU A	Influenza	Amantadine	Rimantadine
RSV	Pneumonia, bronchiolitis	Ribavirin (aerosol)	
HSV	Genital herpes	Acyclovir	Foscarnet
	Keratitis Conjunctivitis	Trifluridine	Idoxuridine Vidarabine
	Encephalitis	Acyclovir	
	Neonatal HSV infection	Acyclovir	Vidarabine
	Herpes infections in immuno-compromised host	Acyclovir	Foscarnet

VZV	In normal host	No therapy	
	In immunocompro-mised host, or during pregnancy	Acyclovir	Foscarnet
CMV	Retinitis	Ganciclovir	Foscarnet
HIV	AIDS HIV antibody positive with CD4 count < 500/mm^3	Zidovudine ± protease inhibitors	Didanosine, Stavudine
HBV **HCV**	Hepatitis B, C	Interferons	