ANTI-VIRAL DRUGS (NON-RETROVIRAL)

Points to be covered in this topic

1. INTRODUCTION
2. CLASSIFICATION OF ANTI- VIRAL DRUGS
3. MOA,PHARMACOKINETICS ,ADR,USES OF DIFFERENT CLASS OF DRUGS

❑ INTRODUCTION

- Viruses are intracellular parasites and depend on the **host cells** for their **food, growth and multiplication.**
- The virus attaches itself to the **host cell membrane** and **penetrates** it (entry), **DNA/RNA is released in the host cell** (uncoating) where it is duplicated
- The viral components are assembled (assembly) and the mature viral particle is then released from the host cell **(budding and release).**

There are two types of viruses—

1. **DNA**
2. **RNA viruses**

The **DNA virus depends on host cell enzymes (mRNA polymerase)** to **synthesize mRNA while RNA viruses** use their own enzymes for mRNA synthesis.

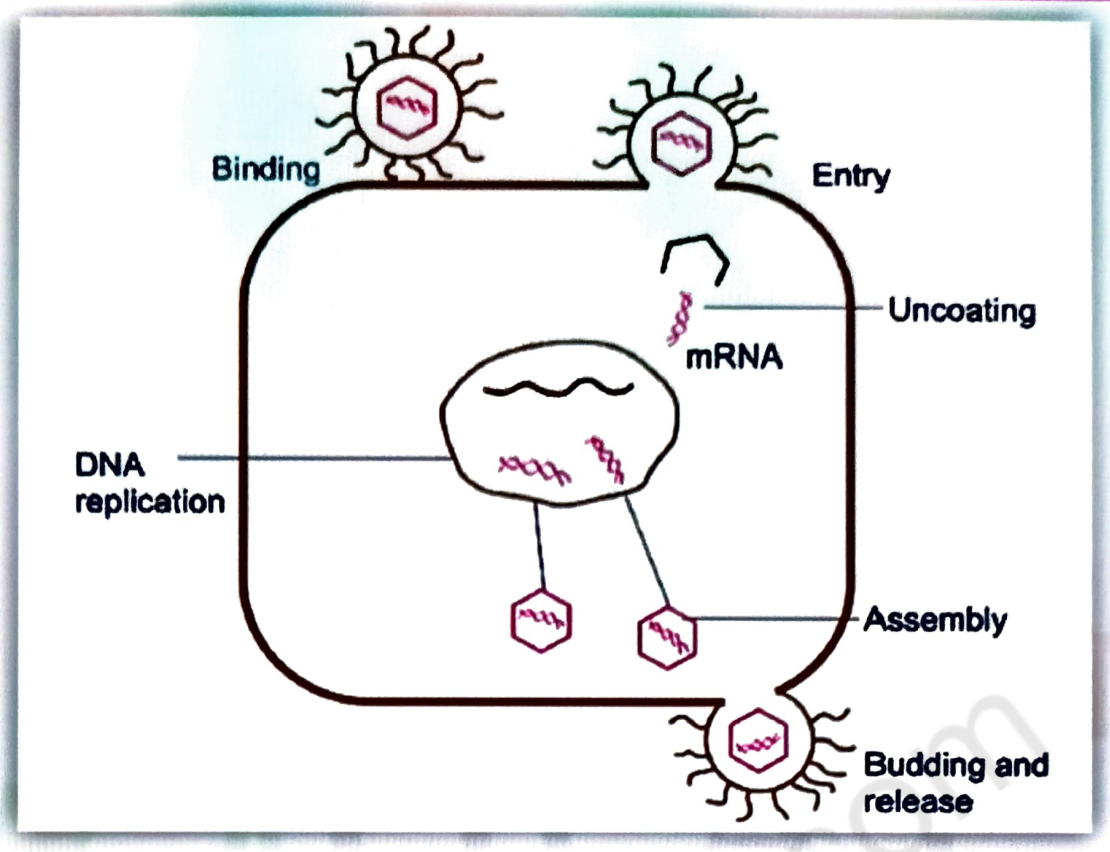


Fig :- Stages of viral replication and sites of action of antiviral drugs

Viral replication steps	*Drugs effective*
Viral attachment and entry	Enfuvirtide, maraviroc, docosanol, palivizumab
Uncoating	Amantadine, rimantadine
Transcription	Interferons
Translation of viral proteins	Fomivirsen, interferons
Nucleic acid synthesis, DNA and RNA replication	Acyclovir, cidofovir, famciclovir, ganciclovir, foscarnet, idoxuridin, NRTIs, NNRTIs, PIs, ribavirin, sorivudine
Assembly	Interferons
Budding and release	Zanamivir, oseltamivir

❖ Retroviruses

- Retroviruses, a type of RNA viruses, are **known to cause AIDS.**
- In retroviruses, a viral enzyme **reverse transcriptase** is involved in replication.
- Two groups of antiviral drugs **inhibit this enzyme.**
- The **immature virion** formed undergoes maturation with the help of the enzyme protease.
- **Inhibitors of this protease prevent maturation of the virions .**

❖ ANTI- VIRAL DRUGS

- Antiviral drugs can act at any **step of viral replication.**
- Viral replication involves **fusion of the virus to host cell membrane** and **penetration inside the cell.**
- Then **uncoating occurs** and early proteins **(like DNA polymerase)** are synthesized.
- The nucleic acids (DNA or RNA) are then synthesized and after that late **proteins (final functional proteins) are synthesized** and processed.
- After packaging and assembly, **viral particles are released** (with the help of neuraminidase) and cause infection of other cells.
- Drugs can act at any of these steps to **inhibit viral replication.**

❑ CLASSIFICATION ON ANTI- VIRAL DRUGS

ANTI-VIRAL DRUGS (Non – retroviral drugs)		
Anti-herpes virus drugs	Idoxuridine , Trifluridine, Acyclovir, Valacyclovir Famciclovir , Ganciclovir , Valganciclovir, Cidofovir Foscarnet	
Anti-influenza virus drugs	Amantadine, Rimantadine ,Oseltamivir ,Zanamivir Peramivir	
Anti-hepatitis virus drugs	For hepatitis B	LamivudineEntecavirAdefovir dipivoxilTenofovirTelbivudine
	For hepatitis C	Ribavirin ,Interferon α, Sofosbuvir ,Simeprevir ,Daclatasvir, Ledipasvir,Velpatasvir

❖ Anti-viral 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**

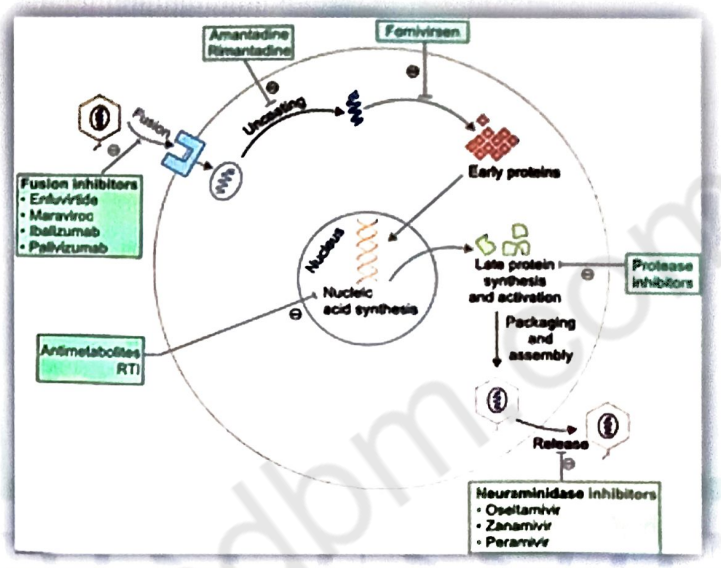


Fig-Mechanism of action of anti-viral drugs

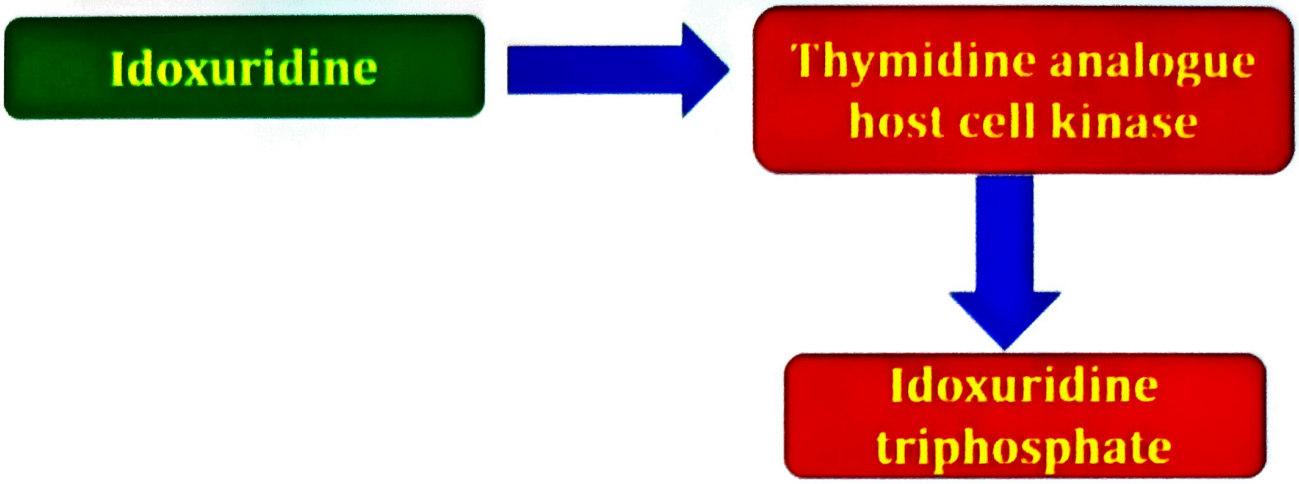
1.ANTI-HERPES VIRUS DRUGS

These are drugs active against the Herpes group of DNA viruses which include **Herpes simplex virus-1 (HSV-1), Herpes simplex virus-2 (HSV2), Varicella-Zoster virus (VZV), Epstein-Barr virus (EBV),** and **Cytomegalovirus (CMV).**

i. Idoxuridine

- It is **5-iodo-2-deoxyuridine (IUDR),** which acts as a **thymidine analogue.**
- It was the **first pyrimidine antimetabolite** to be used as **antiviral drug.**
- It **competes with thymidine**, gets incorporated into viral DNA so that faulty **DNA is formed** which **breaks down easily.**

❖ Mechanism of action



- Use of idoxuridine is restricted to **superficial dendritic keratitis** when rapid action is required.
- Idoxuridine eye drops act **faster than** acyclovir eye ointment, which is more effective when there is stromal involvement of the cornea.
- Ocular irritation occurs with **idoxuridine eye drop**

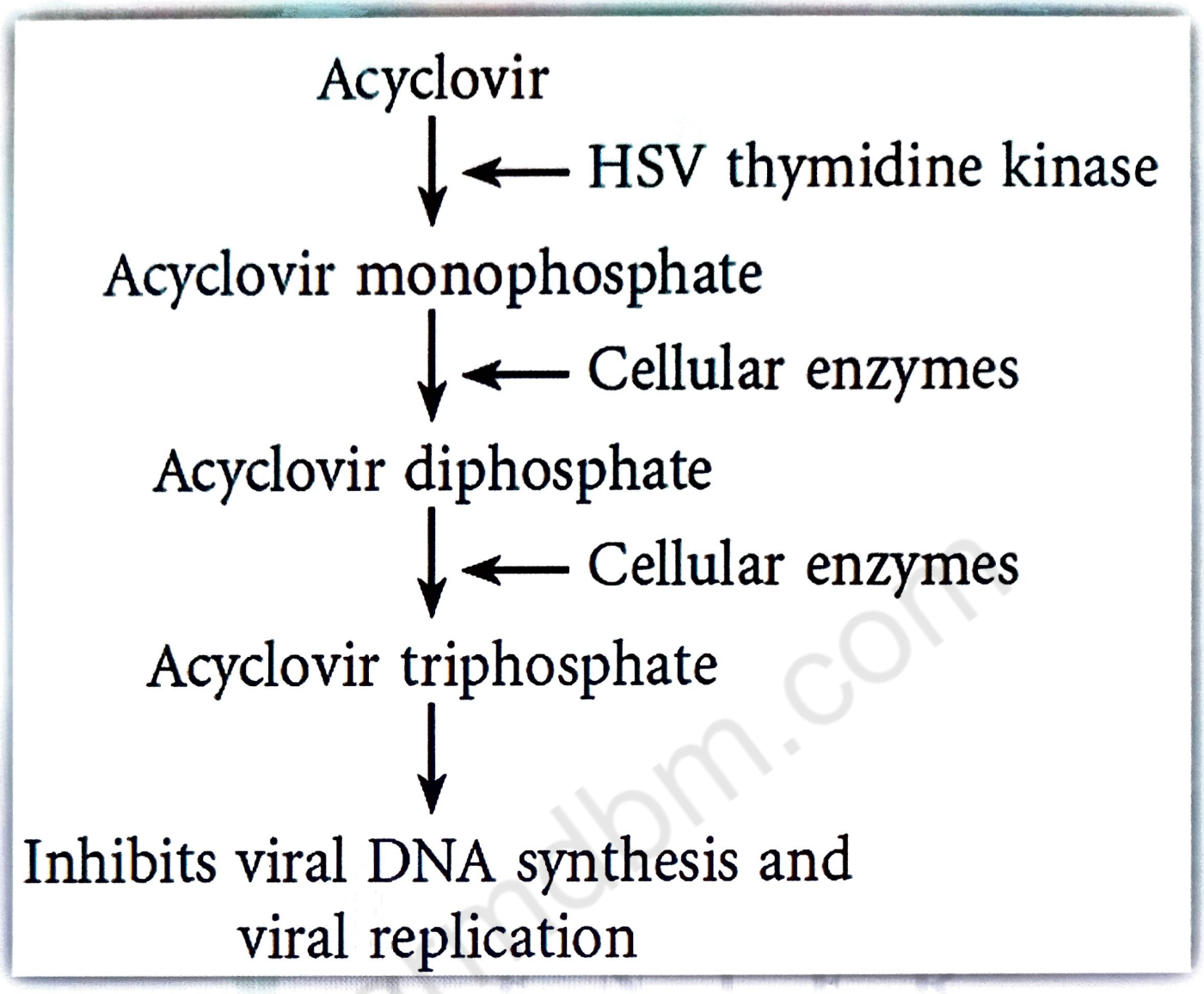
ii.Trifluridine

- It is a fluorinated nucleoside which acts in the same way as idoxuridine, and **inhibits HSV-1, HSV-2, CMV** and related viruses.
- Virus selectivity is **low and DNA synthesis in host cells** is also affected due to **blockade of cellular kinases**.
- Trifluridine eye drop is for use in ***h. Simplex* keratitis.**
- **Higher efficacy** than idoxuridine eye drops .
- **Ocular irritation** and **lid edema** can occur

iii. Acyclovir

- This **deoxiguanosine analogue** requires a virus specific enzyme for **conversion** to the **active metabolite** that **inhibits DNA synthesis** and
- **viral replication.**
- It is **more effective against HSV-1 and HSV-2** than **varicella zoster virus (VZA) infection.**

❖ Mechanism of action



Acyclovir is selectively taken up by the **herpes virus infected cells** and activated to **triphosphate derivative**, which **inhibits viral DNA synthesis.**

❖ Pharmacokinetics

- It is available for **oral, topical and I.V. administration.**
- It is a **highly potent anti herpes drug.**
- It has high therapeutic index with **low toxicity to host cells.**
- Its **oral bioavailability is poor.**
- It is poorly **bound to plasma proteins**, widely distributed in the body,
- It is **crosses BBB**
- Excreted in **urine.**

❖ Adverse effect

- **Nausea, diarrhoea, headache and rashes**
- **Topical acyclovir** can cause **burning** and **irritation.**
- **Given IV,** it may cause **renal and neurotoxicity , hepatic dysfunction**

❖ Uses

i. **Genital Herpes**

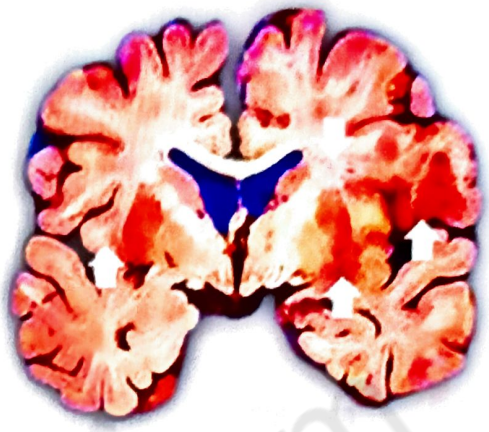
ii. **Herpes Simplex Keratitis**

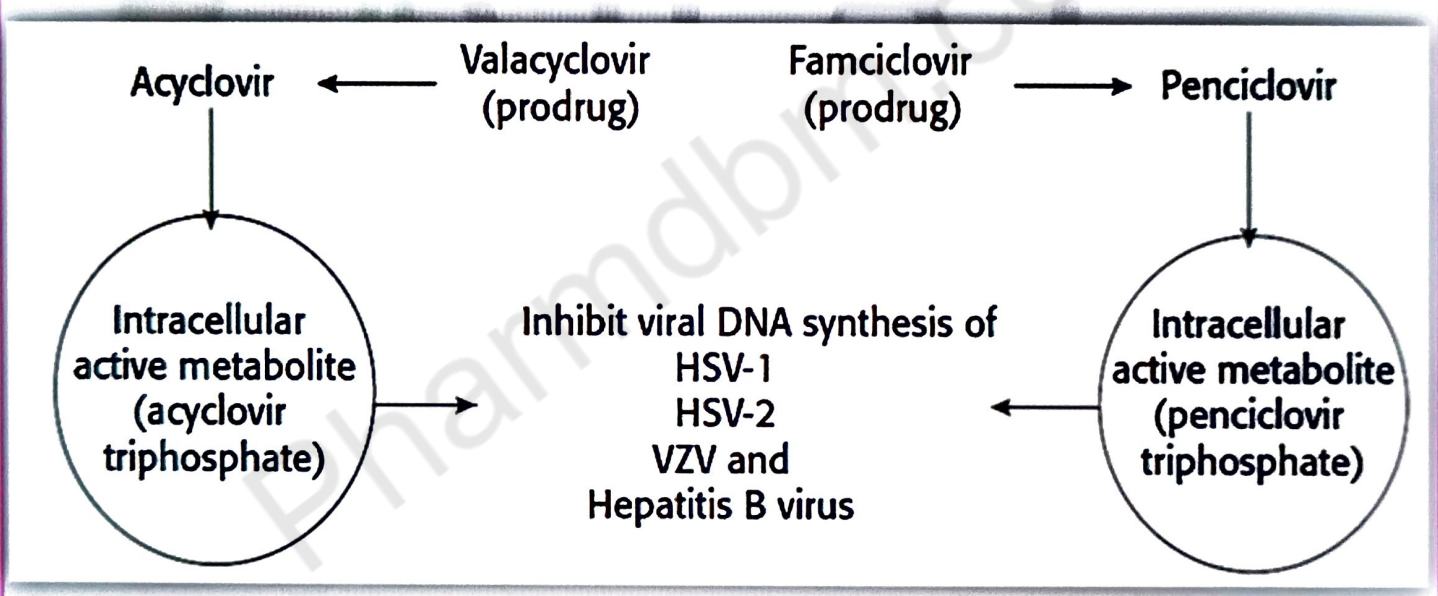
iii. **Herpes Zoster**

iv. **Herpetic encephalitis**

v. **Chickenpox**

vi. **Mycocytanious HSV**





iv. Valacyclovir

- Valacyclovir is a **prodrug of acyclovir** and is rapidly converted to it in the liver.
- High plasma levels of acyclovir are attained.
- It is well tolerated but **high doses used in AIDS**

❖ Pharmacokinetics

- It is a valyl ester prodrug of acyclovir with improved oral bioavailability (55–70%) due to active transport by peptide transporters in the intestine

- During passage through **intestine and liver,** it is completely converted to acyclovir in the first passage by **esterases.**
- Valacyclovir is **excreted in urine** as acyclovir with a **t½ of 3 hours.**

❖ **Adverse effect** :- **Confusion, seizures** and **hallucinations.**

❖ **Uses** :- Valacyclovir is used in herpes simplex, including **genital** and herpes, **herpes zoster** and **CMV disease** like acyclovir

iv. Famciclovir

- Famciclovir is a **prodrug of penciclovir**.
- Famciclovir is **administered orally, well absorbed** and converted to penciclovir in **liver.**
- The mechanism of action **of valacyclovir and famciclovir** are similar to acyclovir.
- Like acyclovir, it needs viral **thymidine kinase** for generation of the active **DNA polymerase inhibitor. Famciclovir inhibits *H. simplex, H. zoster*** but not acyclovir-resistant strains
- Famciclovir has **activity against hepatitis-B virus.**
- It is used as an alternative to acyclovir for **genital** and **herpes zoster**

v. Ganciclovir

- It is an analogue of acyclovir which is **most active against CMV**, but also inhibits other herpes viruses, *viz.* **H.simplex, H. zoster and EBV.**
- Ganciclovir is also activated intracellularly by virus specific **thymidine kinase** and its triphosphate nucleotide preferentially **inhibits viral DNA polymerase.**

vi. Valganciclovir

- It is the **valyl prodrug** of ganciclovir that is **60% bioavailable** orally
- Valganciclovir is also suitable for long term **suppressive therapy of CMV retinitis..**
- It is **indicated for prophylaxis of CMV infections** in **organ transplant/immunosuppressed patients.**
- Adverse effects of **valganciclovir** are similar to **ganciclovir.**

vii. Cidofovir It is a **monophosphate nucleotide analogue of cytidine** which **inhibits most DNA viruses including HSV, CMV, pox and adenoviruses**

❖ Adverse effect

i. **Gastric disturbances**

ii. **Hypersensitivity reactions**

iii. **Neutropenia and uveitis**

viii. Foscarnet

- It is a **pyrophosphate analog** that directly **inhibits viral DNA polymerase and RNA polymerase.**
- It is given IV because of **low bioavailabilty.**
- It attains **good concentrations the CSF**, has a **t½ of about 6 hr** and is excreted by the **kidneys.**
- It may be effective in **CMV colitis** and **oesophagitis.**
- It may be used in other infections like acyclovir resistant herpes infections .

❖ Adverse effects

- Foscarnet **chelates divalent cations** resulting in **hypocalcaemia, hypokalaemia** and **hypomagnesaemia.**

2. ANTI-INFLUENZA VIRUS DRUGS

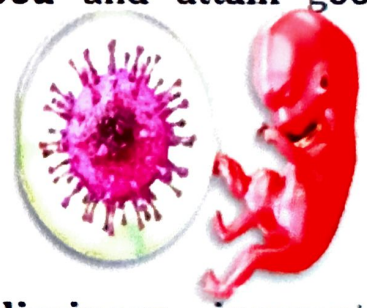
Amantadine, Rimantadine , Oseltamivir , Zanamivir ,Peramivir

i. Amantadine & Rimantadine

- It is an antiviral drug that has **anti Parkinson** effect as well.
- It **inhibits viral replication.**
- Amantadine is used orally for the **prophylaxis** and treatment of **influenza-A virus infection.**
- Amantadine and its derivative **rimantadine inhibit the replication of influenza A viruses.**
- **Rimantadine is more active than amantadine.**
- Rimantadine is the **methyl derivative** of amantadine.
- These drugs **inhibit uncoating of viral RNA and thereby prevent viral replication.**

❖ Pharmacokinetics

- Given **orally**, both of them are **well absorbed** and attain good concentrations in the **nasal secretions and CSF.**
- They are generally well tolerated



❖ Side effect

- ✓ **Nausea, vomiting, diarrhoea, anorexia, dizziness, insomnia,** difficulty in concentrating and ankle oedema
- ✓ Both are **teratogenic.**
- ✓ Rimantadine is **longer-acting** and has **fewer adverse effects.**

❖ Uses

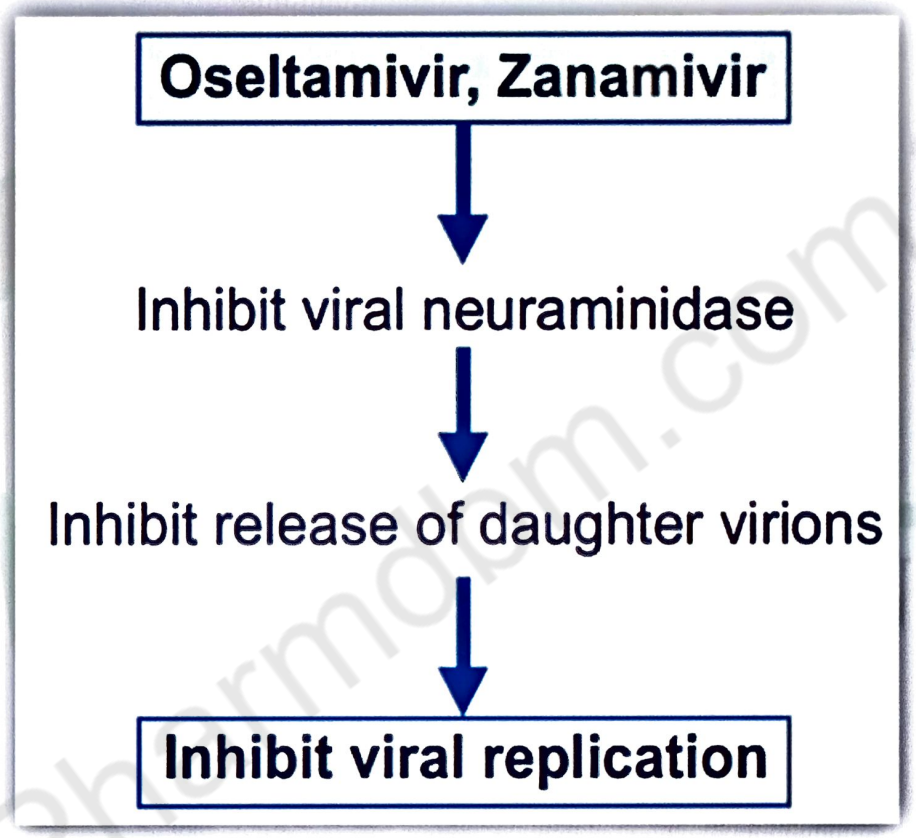
i. Treatment of influenza A

ii. Prophylaxis of influenza A & Parkinsonism

ii. Oseltamivir

- This is the most commonly used **anti-influenza virus drug** .
- It is a sialic acid analogue with **broad spectrum activity** covering **influenza A** (amantadine sensitive as well as resistant), **H5N1** (bird flu), **H1N1** (swine flu)strains and **influenza B.**

❖ Mechanism of action



- They inhibit viral replication by **inhibiting the neuraminidase** activity which is essential for the release of **daughter virions.**
- **Oseltamivir** and **zanamivir** are effective against **both influenza A including H1N1 and influenza B.**

❖ Pharmacokinetics

- Oseltamivir is **given orally.**
- It is a prodrug, **well absorbed from the gut** and activated in the **liver by esterases**

❖ Adverse effects

- **Nausea, vomiting** and **abdominal discomfort.**

iii. Zanamivir

- **Influenza A (including amantadine-resistant, H1N1, H5N1 strains)** and **influenza B virus neuraminidase inhibitor** that is administered by **inhalation** as a **powder** due to very **low oral bioavailability.**
- Small amount that is **absorbed after inhalation** is **excreted by the kidney with a t½ of 2–5 hours.**
- The mechanism of action, clinical utility and efficacy of zanamivir are similar to oseltamivir.

❖ Uses

- Oseltamivir and zanamivir are used in the prevention and treatment of influenza **including H1N1 infection.**

iv. Peramivir

- Peramivir is **active against human influenza A and B**, as well as **bird flu (H5N1), swine flu (H1N1)** and several emerging strains of **influenza A** virus, including those resistant to oseltamivir.
- Peramivir is **more active in vitro against influenza B**, which is intrinsically less susceptible to **oseltamivir** and **zanamivir.**

3. ANTI-HEPATITIS VIRUS DRUG

❖ Drugs uses for hepatitis B

Lamivudine ,Entecavir ,Adefovir dipivoxil, Tenofovir ,Telbivudine

i. Lamivudine

Lamivudine (3TC) :- This **deoxycytidine analogue** is **phosphorylated intracellularly** and **inhibits HIV reverse transcriptase** as well as **HBV DNA polymerase.**

❖ Pharmacokinetics

- Oral bioavailability of **3TC is high and plasma t½ longer (6–8 hours).**

- **Intracellular t½ is still longer (> 12 hr).**
- It is mainly **excreted unchanged in urine.**

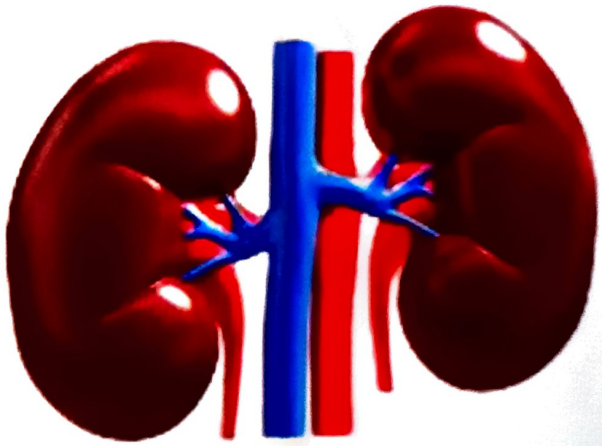
Lamivudine used in **antiretroviral therapy** has the following advantages in HBV:

1. **Long intracellular t½ in HBV infected cells.**
2. It can be given even in patients with **liver disease.**
3. It has shown efficacy in **prevention of vertical transmission** from **mother to fetus.**

ii. Entecavir

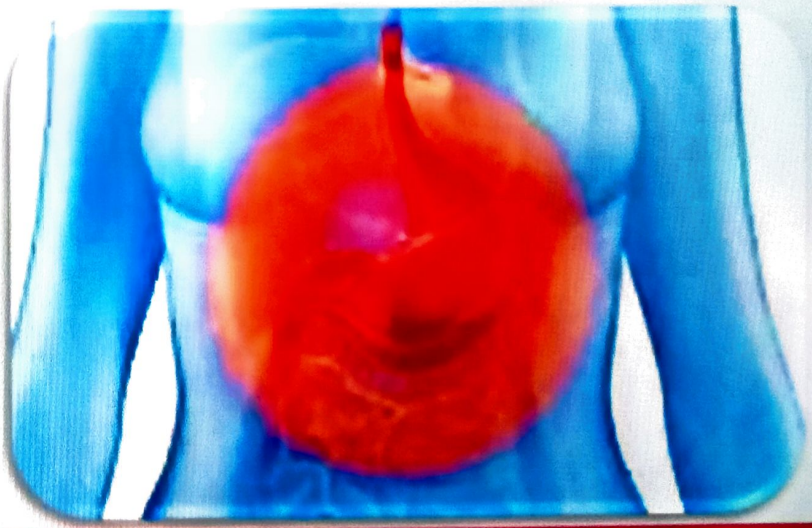
- Entecavir is a **guanosine nucleoside** analog that **inhibits DNA polymerase**.
- Entecavir **inhibits HBV DNA polymerase** after **activation by intracellular phosphorylation.**

❖ Pharmacokinetics



- It is completely absorbed on **oral administration**, but should be given on an empty stomach.
- It is well tolerated.
- Excreated by the **kidney**
- Entecavir is useful in **chronic HBV infection**

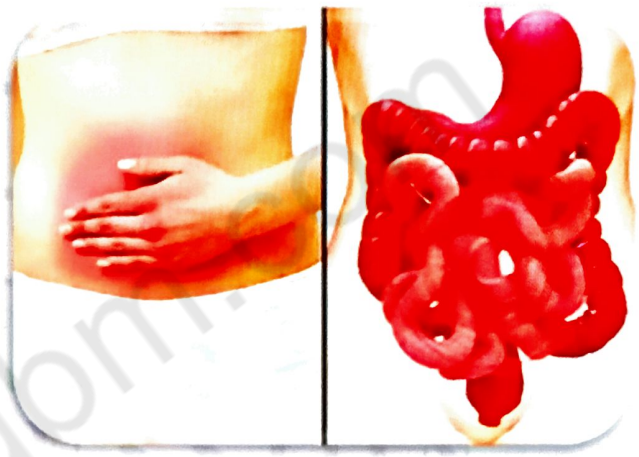
❖ Side effects



- **Mild dyspepsia**
- **Nausea, diarrhoea**
- **Fatigue,**
- **Disturbed sleep.**

iii. Adefovir dipivoxil

- Adefovir is a **monophosphate analogue of AMP** that is **active against HBV** and some other **DNA as well as RNA viruses**, but is used only for **hepatitis caused by HBV.**
- Esterases in the **intestine** and **liver release the active drug** during absorption to attain oral bioavailability of ~60% in terms of Adefovir On entering cells, **adefovir is phosphorylated** to the **diphosphate** which has **high affinity for HBV DNA polymerase** compared to **host cell DNA polymerase**



❖ Side effects

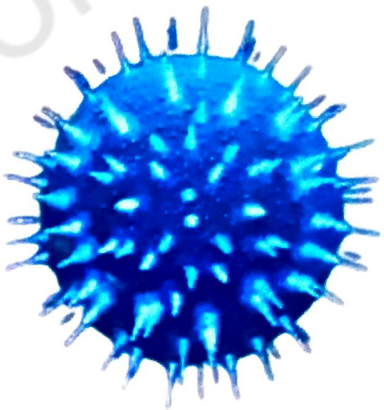
- **Sore throat**
- **Headache**
- **Weakness**
- **Abdominal pain & flu syndrome.**

iv. Tenofovir

- It is **a monophosphate nucleotide** related to AMP, which is **active against HBV as well as HIV.**
- Due to very low **oral absorption.**
- it is used as the **disoproxil ester prodrug**, which not only improves bioavailability, but also intracellular passage of the active form.
- Tenofovir released from **hydrolysis of the prodrug is diphosphorylated** by cellular kinases into tenofovir diphosphate which preferentially **inhibits HBV-DNA polymerase** and **HIV-reverse transcriptase.**
- Affinity for host DNA-polymerase is **very low.**
- It also gets incorporated in the **viral DNA to cause chain termination**

v. Telbivudine

- Anti-HBV drug is a **thymidine nucleoside analogue**.
- Telbivudine is **absorbed orally** and its bioavailability is not affected by food.
- It is **not metabolized** and is excreted unchanged by the kidney with an average **plasma t½ of 15 hours**.
- Telbivudine enters cells and is **phosphorylated by cellular kinases** to generate the **active triphosphate nucleotide**, which competitively **inhibits HBV DNA polymerase**, and also gets incorporated into HBV-DNA resulting in **chain termination.**
- Telbivudine causes faster and more complete **suppression of HBV-DNA** titre than lamivudine or Adefovir , but resistance often develops resulting in **return of viraemia.**



- Telbivudine-resistance is more likely in **lamivudine-resistant cases**.
- As such, it not a **first line drug for chronic hepatitis B**.
- **Tolerability of telbivudine** is good

❖ Side effects

i. **Abdominal pain**
ii. **Diarrhoea**
iii. **Cough**
iv. **Headache**
v. **Dizziness**
vi. **Myalgia**

❖ Drugs uses for hepatitis B

Ribavirin , Interferon α , Sofosbuvir ,Simeprevir ,Daclatasvir, Ledipasvir, Velpatasvir

i. Ribavirin

- **Purine nucleoside analogue** has broad-spectrum antiviral activity, including that against **HCV, influenza A and B,** respiratory syncytial virus and many other **DNA and double stranded RNA viruses**.
- Its **mono- and triphosphate derivatives** generated intracellularly by **host kinases inhibit GTP synthesis** and **viral RNA synthesis.**

❖ Pharmacokinetics

- Oral bioavailability of ribavirin is ~50%.
- It is partly metabolized and eliminated mainly by the kidney.

❖ Uses

- Oral ribavirin is used in **chronic hepatitis C,** but it is not used alone.
- Nebulized ribavirin is used for **respiratory syncytial virus bronchiolitis** in **infants and children**, particularly those with **congenital heart disease**, **prematurity** or other high risk conditions.

❖ Side effects :- Haemolytic anaemia., Bone marrow, depression, CNS

ii. Interferon α

Interferons (IFNs) are **low molecular weight glycoprotein cytokines** produced by host cells in response to viral infections, TNFα, IL-1 & some other inducer.

❖ Mechanism of action

Interferons **bind to specific receptors** and **activate JAK-STAT pathway** and thereby stimulate the synthesis of certain proteins which **inhibit viral protein synthesis.**

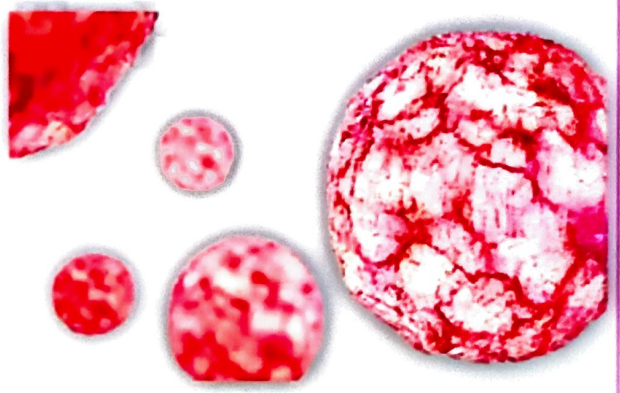
Interferon- α acts on multiple stages of viral replication including **inhibition of viral penetration**, **protein synthesis**, **maturation** and release.

❖ Pharmacokinetics

- After **I.M./S.C.** Injection, interferon is distributed to tissues.
- It is degraded mainly in **kidney** and to some extent in liver.
- Plasma for **< 24 hours.**

❖ Adverse effects

- ✓ **Flu-like symptoms** —**Fatigue, aches** and **pains, malaise, fever, dizziness, anorexia, nausea, taste** and **visual disturbances**
- ✓ **Neurotoxicity** —**Numbness, neuropathy**, altered behaviour, **mental depression, tremor, sleepiness**, rarely convulsions.
- ✓ **Myelosuppression** : **Neutropenia, thrombocytopenia.**
- ✓ **Thyroid dysfunction** (hypo as well as hyper).
- ✓ **Hypotension**, transient arrhythmias, alopecia and reversible liver dysfunction.

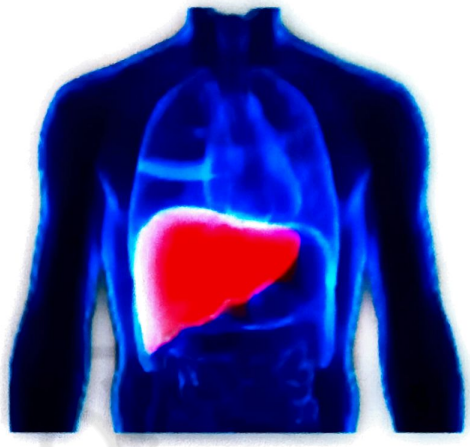


❖ Uses

i. **Chronic hepatitis B**
ii. **Chronic hepatitis C**
iii. **AIDS-related Kaposi's sarcoma**
iv. **Condyloma acuminata**
v. **H. simplex, H. zoster and CMV**
vi. Interferons are also used in **chronic myeloid leukaemia, follicular lymphoma, cutaneous T-cell lymphoma and multiple myeloma.**

iii. Sofosbuvir

- It is activated to its triphosphate derivative which when given orally **inhibits RNA-dependent RNA polymerase.**
- Sofosbuvir is used in combination with peg **IFN-α** and ribavirin to attain high cure rates.
- It is given orally and is well tolerated.



❖ Pharmacokinetics

- Oral bioavailability of **Sofosbuvir is ~80%**
- It is rapidly metabolized in **liver**
- Excreted in **urine**
- **t½ of 27 hr.**

❖ **Side effect** are **fatigue** and **headache, bradycardia , joint pain .**

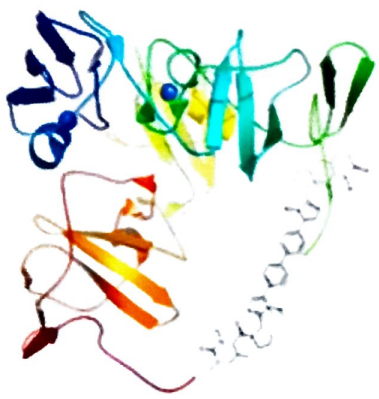
iv. Simeprevir

- **Boceprevir, Simeprevir and Telaprevir inhibit HCV protease** and are used in combination with **IFN_S and ribavirin.**
- All are orally effective, are to be taken with Food and are **metabolized by CYP3A4** which could result in drug interactions

❖ **Side effect** are **fatigue** and **headache, bradycardia , joint pain, photosensitivity**

v. Daclatasvir

- It is an orally **active NS5A inhibitor** which **blocks HCV-RNA replication** as well as assembly of progeny virions.
- **Daclatasvir is metabolized by CYP3A** and is a substrate for **efflux transporter Pgp.**
- It also **inhibits Pgp** and other transporters.



It is active against all genotypes of HCV.

The t½ of daclatasvir is 12–15 hr.

It is generally well tolerated.

❖ **Adverse effects** are headache, fatigue, abdominal pain, alopecia, anaemia and rarely allergy.

vi. Ledipasvir

- Ledipasvir is **metabolized.**
- It is largely excreted unchanged in **faeces.**
- The **t½ is 48 hr.**
- The **LDV/SOF** combination should not be used in patients being treated
- with **Pgp inducers.**

vii. Velpatasvir

- It is partly **metabolized** and excreted mainly in **faeces.**
- **t½ is 15 hours .**
- **Inducers of CYP3A** and **Pgp lower Velpatasvir blood levels** and should not be used with it.

❖ **Adverse effects** are **headache, fatigue, weakness and nausea**

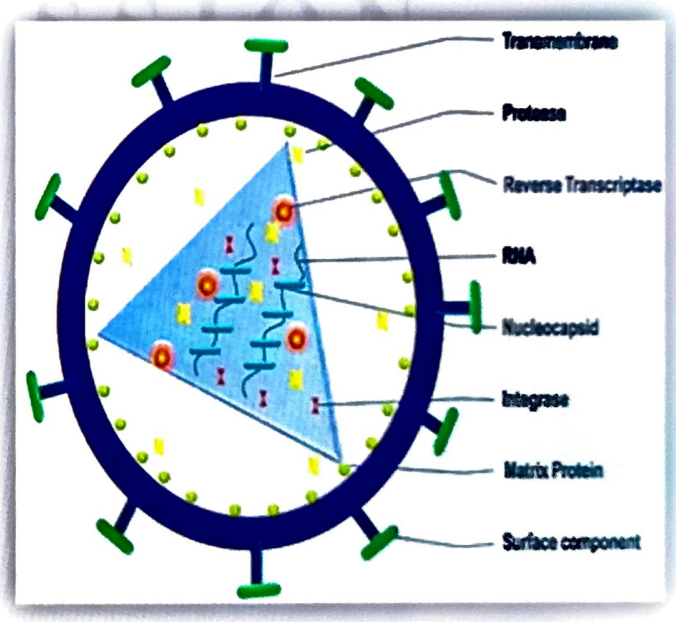
ANTI-RETEROVIRAL DRUGS

Points to be covered in this topic

1. INTRODUCTION
2. CLASSIFICATION OF ANTIRETEROVIRAL AGENTS
3. MOA,PHARMACOKINETICS, ADR, USES OF DIFFERENT CLASS OF DRUGS
4. TREATMENT OF HIV

❑ INTRODUCTION

- A retrovirus is a type of **RNA virus that inserts a copy of its genome** into the **DNA of a host cell** that it invades, thus **changing the genome of that cell.**
- These against are drugs **active human immunodeficiency(HIV) VIRUS** which is a retrovirus .



- **Acquired immunodeficiency syndrome (AIDS)** results from infection with **human immunodeficiency virus (HIV)—a retrovirus.**
- These are drugs active **against human immunodeficiency virus (HIV)** which is a retrovirus.

➢ Two types of HIV have been identified **HIV-1 and HIV-2.**

HIV-1	HIV-2
This strain is found worldwide and is more common	This strain is found predominantly in West Africa.
This strain is more likely to progress and worsen.	This strain is less likely to progress and many of those infected remain lifelong non progressors
Average level of immune system activation are higher.	Average level of immune system activation are lower
During progression, HIV-1 has lower CD4 counts than HIV-2.	During progression, CD4 counts are higher in this strain.
Plasma viral loads are higher.	Plasma viral loads are lower

❖ ANTIRETROVIRAL DRUGS

The clinical efficacy of anti retrovirus drugs is monitored primarily by **plasma HIV-RNA assays and CD4 lymphocyte** count carried out at regular intervals.

➢ The two established targets for anti-HIV attack are

❖ **HIV reverse transcriptase**: **Which transcripts HIV-RNA into proviral DNA.**

❖ **HIV-integrase : Viral enzyme which integrates the proviral DNA into host DNA.**

❖ **HIV protease: Which cleaves the large virus directed polyprotein into functional viral proteins.**

❖ **Fusion** of **viral envelope with plasma membrane of CD4 cells** through which **HIV-RNA enters the cell.**

❖ **Chemokine coreceptor (CCR5) on host cells** which provide for the surface **proteins of the virus.**

❑ CLASSIFICATION OF ANTI-RETEROVIRAL AGENTS

CLASS	DRUGS
Nucleoside reverse transcriptase Inhibitors (NRTIs)	Zidovudine, Didanosine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Tenofovir
Non-nucleoside reverse transcriptase Inhibitors (NNRTIs)	Nevirapine, Efavirenz, Delavirdine, Etravirine, Rilpivirine
Protease inhibitors (Pls)	Ritonavir, Atazanavir, Indinavir, Nelfinavir, Saquinavir Fosamprenavir, Lopinavir, Darunavir
Entry inhibitor	Enfuvirtide (T-20)
CCR-5 receptor inhibitor	Maraviroc
Integrase inhibitor	Raltegravir , dolutegravir (DTG)

1.Nucleoside reverse transcriptase Inhibitors (NRTIs)

- These **drugs after entering.**
- HIV infected cells, are **converted to active triphosphate ZIDOVUDINE formed by cellular kinase** and **competitively inhibits HIV reverse transcriptase.**
- They get incorporated into **the growing viral DNA** and cause **termination of chain elongation of proviral DNA.**

Zidovudine, Didanosine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Tenofovir

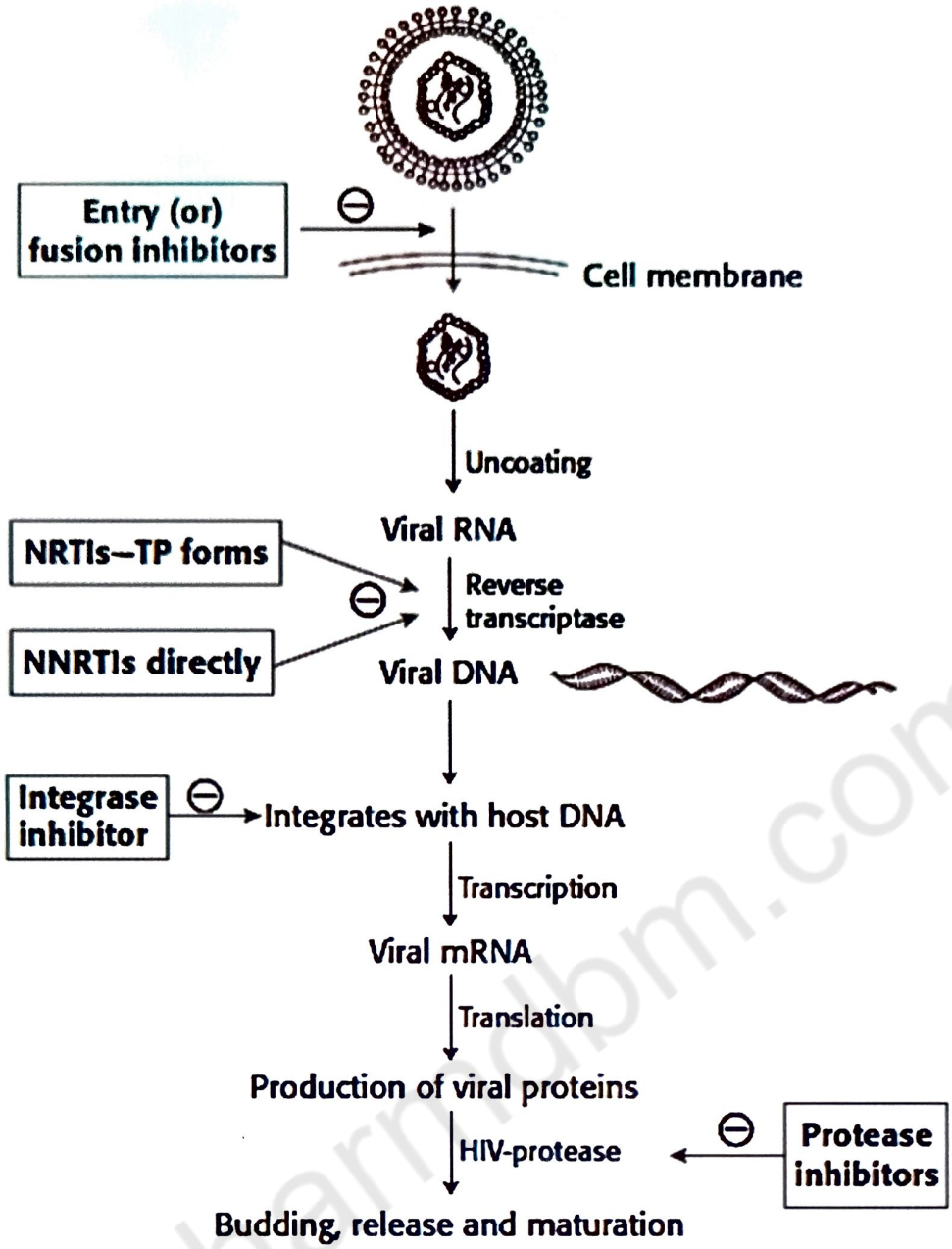


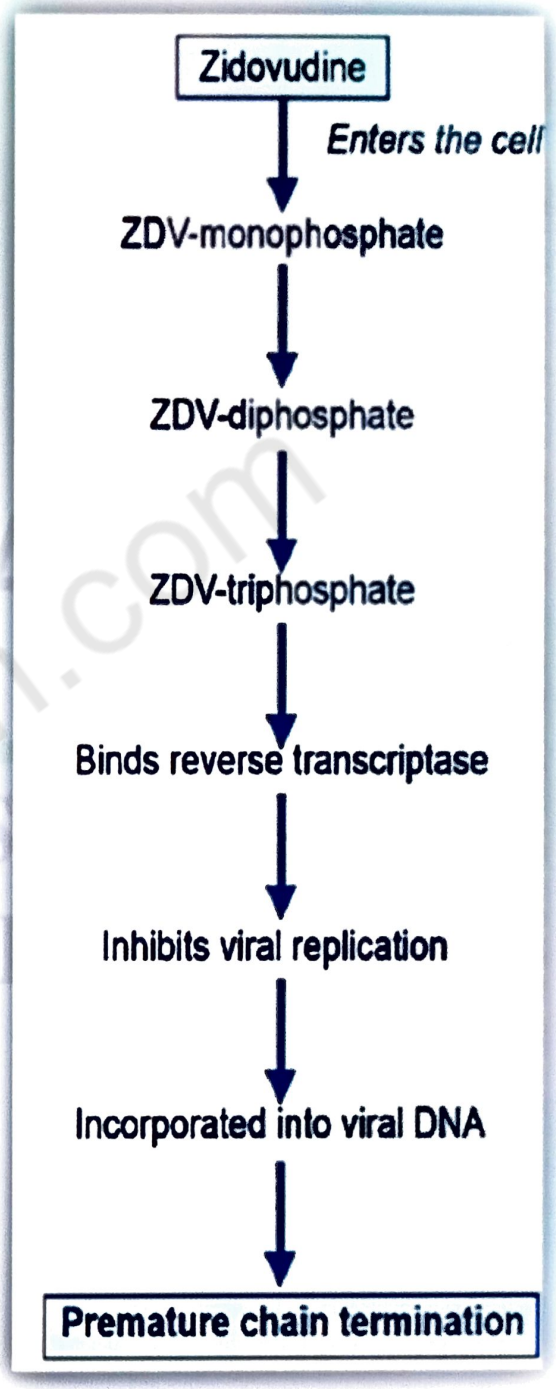
Fig :- Steps in the life cycle of HIV with sites of action of antiretroviral drugs

1. Zidovudine

- Zidovudine was the **first antiretroviral drug** approved for the treatment of **HIV infection.**
- It is the **prototype drug of NRTIs.**
- Zidovudine is **effective against HIV-1 and HIV-2.**
- It protects the **uninfected cells from HIV**, but has **no effect on HIV-infected cells.**
- Zidovudine is a **thymidine analog**, **active against HIV infections** and other retroviruses.

❖ Mechanism of action

- Zidovudine phosphorylated in **the host cell -zidovudine triphosphate** selectively **inhibits viral reverse transcriptase** in preference to **cellular DNA polymerase.**
- **NRT inhibitors enter the cells** and are converted to their corresponding **triphosphate derivatives** which have a **high affinity for reverse transcriptase**, an **enzyme specific to HIV and required for DNA synthesis**.
- The **NRT inhibitors are nucleoside analogs.**
- They **competitively inhibit reverse transcriptase**, are incorporated into **viral DNA chain and terminate DNA chain elongation.**
- **Tenofovir is a nucleotide analog** and **competitively inhibits HIV reverse transcriptase** similar to nucleoside analogs.



❖ Resistance

- when AZT was used alone, **>50%** patients became nonresponsive to AZT within 1-2 years therapy due to growth of **resistant mutants.**

❖ Pharmacokinetics

- Oral absorption of AZT is rapid, but **bioavailability is ~65%.**
- Cleared by **hepatic glucuronidation (t½ 1 hr)**

- **Excreted in urine- Plasma protein binding is 30%** and CSF level is ~50% of that in plasma.
- It crosses **placenta** and is found in **milk**

❖ Adverse effect

i. **Anaemia,**

ii. **Granulocytopenia**

iii. **Myopathy, peripheral neuropathy and pancreatitis.**

iv. **Lactic acidosis** and **hepatic steatosis** are rare but can be fatal.

v. Toxicity is due to **inhibition of DNA polymerase in human cells** though to a small extent

vi. **Bone marrow suppression**

❖ Uses

i. Zidovudine is used in **combination with other antiretroviral drugs** for the **treatment of AIDS.**

ii. It is also used for **post-exposure prophylaxis (PEP)** and to prevent vertical transmission of HIV.

ii. Didanosine

- It is a **purine nucleoside** analogue which after **intracellular conversion to didanosine triphosphate competes with ATP** for incorporation into viral DNA,
- **Inhibits HIV reverse transcriptase** and terminates proviral DNA.
- Mutational resistance develops, but only few AZT **resistant mutants are non-responsive to didanosine** also.
- It is infrequently used now due to **higher toxicity than other NRTIs.**
- It can be given **once daily** because the drug remains intracellularly for a long time.

- Pancreatitis is dose-dependent

Side effect:- Diarrhoea, abdominal pain, dry mouth and nausea

iii. Stavudine

- It is also a **thymidine analogue** which acts in the same way as **AZT.**
- Because of long term serious metabolic complications like **lipodystrophy, lactic acidosis** and **peripheral neuropathy** stavudine is no longer

IV. Lamivudine (3TC)

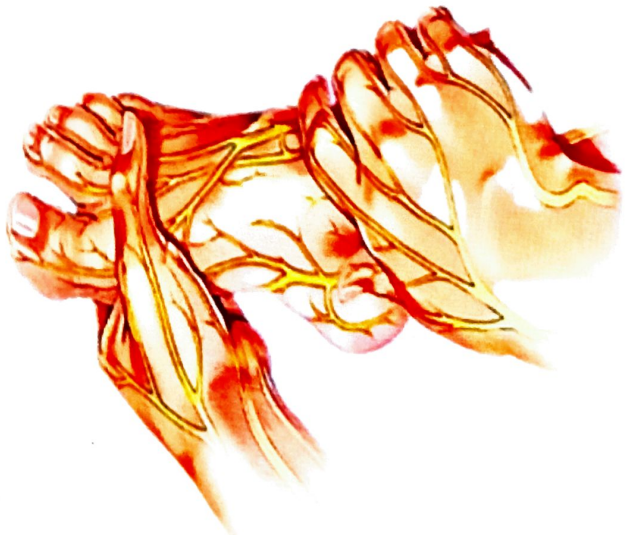
- This **deoxycytidine analogue** is **phosphorylated intracellularly** and **inhibits HIV reverse transcriptase** as well as **HBV DNA polymerase**.
- Its incorporation into viral DNA results in **chain termination.**
- Most human **DNA polymerases** are not affected and systemic toxicity of 3TC is low. Point mutation in **HIV-reverse transcriptase and HBV-DNA polymerase** gives rise to rapid lamivudine resistance.

❖ Pharmacokinetics

i. **Oral bioavailability** of 3TC is high
ii. **plasma t½ longer (6–8 hours).**
iii. Intracellular t½ is still longer (> 12 hr).
iv. It is mainly excreted unchanged in **urine.**

❖ Adverse effects

i. **Peripheral neuritis**
ii. **Pancreatitis**
iii. **Gastrointestinal disturbances**
iv. **Lactic acidosis**
v. **Skin rashes**



V. Abacavir (ABC)

- This **guanosine analogue** is a clinically potent ARV drug that acts after **intracellular conversion to carbovir triphosphate**, which gets incorporated in proviral DNA and terminates chain elongation.

❖ Pharmacokinetics

- Its oral bioavailability is **80%** and it is mainly eliminated by **metabolism.**
- The plasma **t½ is 1–1.5 hour,** but intracellular t½ of the active metabolite is >12 hours.

❖ Adverse effects

- **Hypersensitivity reactions such as rashes, fever**
- **Abdominal pain**
- **Bowel upset**
- **Flu-like respiratory**

VI. Tenofovir (TDF)

- It is an **adenosine analog.**
- It is **converted to tenofovir diphosphate** which is incorporated into **reverse transcriptase** and causes **termination of the chain.**
- Tenofovir is used as an alternative in the **treatment of HIV infections** in combination with other drugs.

vii. Emtricitabine (FTC)

❖ Mechanism of action

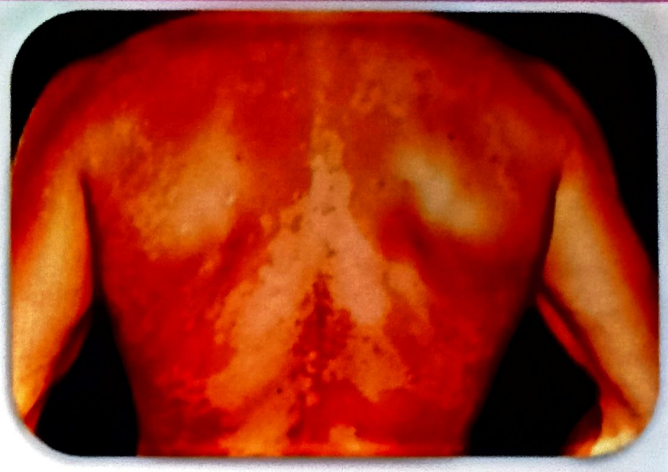
- It is a **fluorinated cytidine analogue** which is converted **intracellularly by cellular kinases** into its **triphosphate** which acts as the **HIV reverse transcriptase inhibitor**

❖ Pharmacokinetics

- Emtricitabine is **well absorbed orally** metabolized largely excreted unchanged by the **kidney** with **a t½ of 10 hrs.**

❖ Side effects

- Fatigue
- Headache
- Nausea
- Diarrhoea
- Discoloration of exposed skin



MOA of Didanosine, Stavudine, Emtricitabine and Lamivudine

Didanosine
Stavudine
Zalcitabine
Lamivudine
Emtricitabine

→ **Transported into cells and activated to respective triphosphate forms**

→ **Inhibit HIV reverse transcriptase**

→ **DNA chain termination**

2. Non-nucleoside reverse transcriptase Inhibitors (NNRTIs)

- NNRTIs are **highly active against HIV-1** but have **no effect on HIV-2.**
- There is **no cross-resistance with the NRTIs.**
- They are used in combination with **NRTIs in the treatment of AIDS.**

Nevirapine, Efavirenz, Delavirdine, Etravirine, Rilpivirine

❖ Mechanism of action

Nevirapine, Delavirdine Efavirenz

Bind directly to reverse transcriptase enzyme and inhibit their function(Do not require intracellular phosphorylation)

i.Nevirapine (NPV)

❖ Pharmacokinetics

- It is **well absorbed orally >90% bioavailability**, attains high levels in CSFAnd has a **long t½.**
- Fatty food enhances the absorption and also toxicity hence, it should be taken on empty stomach.
- It is metabolised by the microsomal enzymes **CYP3A4** in the liver.

❖ Adverse effect

- **Allergic reactions ranging from skin rashes**
- **Pruritus to stevens-johnson syndrome and toxic epidermal necrolysis** can Occur.

❖ Uses

i. Nevirapine is used in the **treatment of HIV-1 infections** in combination with other drugs.

ii. Nevirapine is effective in a single dose (200 mg) at the onset of labour and in newborn 2 mg/kg single dose within 3 days of **birth to prevent vertical transmission from the mother to the newborn.**

ii. Efavirenz

❖ Pharmacokinetics

- It has an **oral bioavailability of 50%.**
- It is **99% bound to plasma proteins.**
- It is **metabolised by the microsomal enzymes.**

❖ Side effects

i. **Headache, dizziness, drowsiness, nightmares, confusion, vomiting**

ii. **Diarrhoea and skin rashes.**

iii. Efavirenz has **teratogenic effects in monkeys** and is **contraindicated in pregnant women.**

❖ Uses

- Efavirenz is used in the treatment of **HIV-1 infection** in combination with other antiretroviral drug

iii. Etravirine

- It is effective in **HIV-1 that is resistant to other NNRTIs.**
- It is well tolerated—can cause **nausea, diarrhoea, skin rashes and raised liver enzymes.**
- Etravirine is also metabolised by **microsomal enzymes**, **inhibits some (like CYP 2C9 and CYP 2C19) and induces some others like CYP3A4**

iv. Rilpivirine

- It is **effective against HIV-1 resistant to other NNRTIs.**

❖ Drug Interactions of NNRT Inhibitors

i. Nevirapine is a microsomal **enzyme inducer** . Concurrent administration of **rifampicin and ketoconazole** should be **avoided.**

ii. Delavirdine is a microsomal **enzyme inhibitor.**

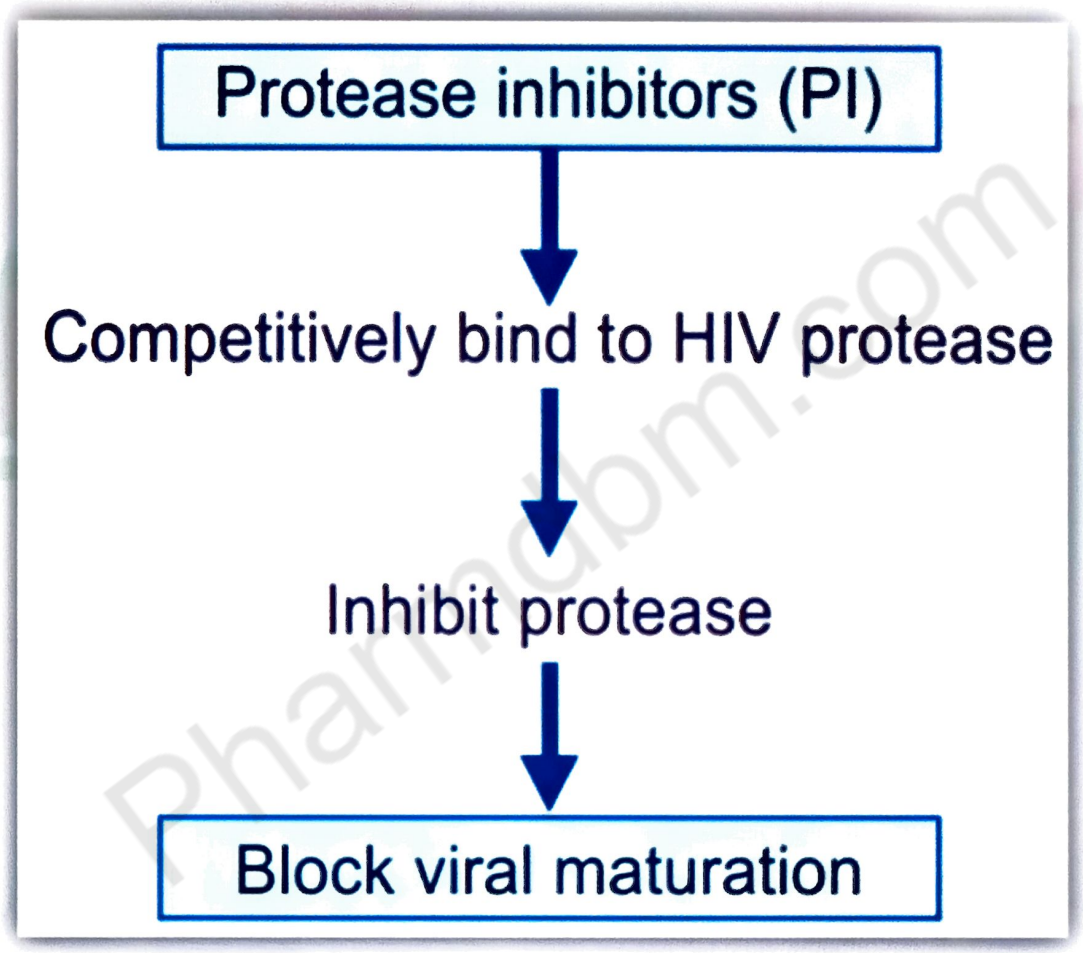
It also increases plasma levels of protease inhibitors like **saquinavir** and **indinavir**

3. Protease inhibitors (PIs)

Ritonavir, Atazanavir, Indinavir, Nelfinavir, Saquinavir Fosamprenavir, Lopinavir, Darunavir

- Protease inhibitors have been used with other antiretroviral drugs.
- **Saquinavir** is the first agent to be used in this group

❖ Mechanism of action



- They competitively **inhibit the HIV protease enzyme** ⟶ **prevent cleavage of viral poly proteins** to the final functional, structural and enzymatic components of HIV ⟶ **immature and non infectious** viral particles are produced.

✓ **Cross-resistance** is common among the PIs, but there is no cross-resistance with reverse transcriptase inhibitors.

- PIs are used orally with **reverse transcriptase inhibitors** in patients with AIDS.

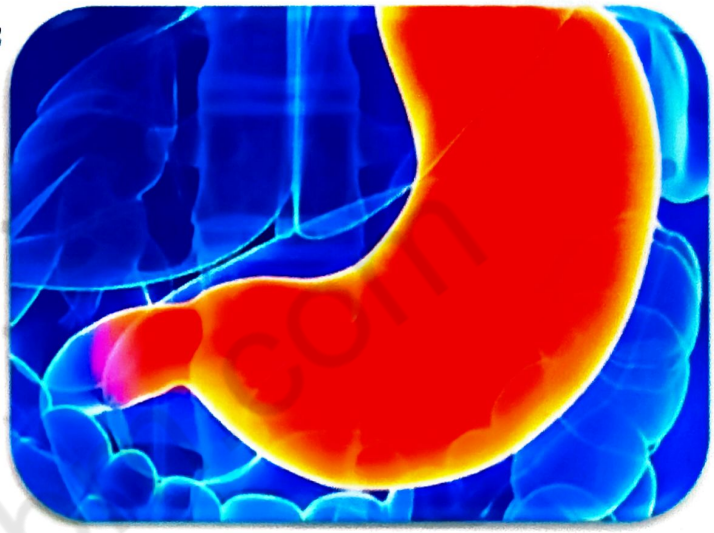
i. Ritonavir (RTV)

❖ Pharmacokinetics

- It is well absorbed and metabolised by microsomal enzymes like **CYP3A4.**
- It is a powerful **enzyme inhibitor.**

❖ Adverse effect

- **Gastrointestinal disturbances**
- **Nausea**
- **Diarrhoea**
- **Paresthesias , fatigue**
- **Lipid abnormalities**



ii. Atazanavir (ATV)

❖ Pharmacokinetics

- This PI is administered with **light meal which improves absorption,** while acid suppressant drugs decrease its absorption.
- ATV is **metabolized primarily by CYP3A4**, which is also moderately inhibited by it.
- Bioavailability and efficacy of ATV is improved by combining with RTV.
- **t½ is 6–8 hours.**

❖ Side effects:- Loose motions, nausea and abdominal pain.

iii. Indinavir(INV)

- Indinavir is absorbed in **presence of acidic medium** and should be given on an **empty stomach.**
- It can cause **GI disturbances and renal stones** —enough water intake needed.

iv.Nelfinavir (NFV)

- It is to be taken with meals, since **food increases absorption**, but **bioavailability is erratic.**
- NFV is mainly **metabolized by CYP2C19.**

❖ **Side effect :- Diarrhoea and flatulence.**

v. Saquinavir (SQV)

- Its **oral bioavailability is low**, the tablet.
- But **fatty food increases absorption by >5 times**
- It is a **weak inhibitor of CYP3A4.**

❖ **Side effects :-**

i. **Photosensitivity**

ii. **GI disturbances**

vi. Fosamprenavir (FPV)

- It is a **phosphorylated prodrug** of amprenavir that has better **oral bioavailability** and better tolerability than the parent drug.
- As such, it has **replaced amprenavir.**
- Fosamprenavir is **active against both HIV-1 and HIV-2**, and is effective in treatment-naive as well as previously PI treated patients.

❖ **Pharmacokinetic**

- It is extensively metabolized, mainly by **CYP3A4** and is a moderate inhibitor of CYP3A4.
- The plasma t½ is ~8 hours.

❖ **Side effects**

i. **Nausea**

ii. **Diarrhoea**

iii. **Fatigue and Rashes**

vii. Lopinavir(LPV)

- Lopinavir is given along with **ritonavir (LPV/r)—effective against both HIV-1 and HIV-2.**
- CYP3A4 inhibitor.
- It should be given with food.
- Lopinavir **should not be** given concurrently with **fosamprenavir , rifampicin and alcohol**
- **Lopinavir + Ritonavir ⟶ improve bioavailability**

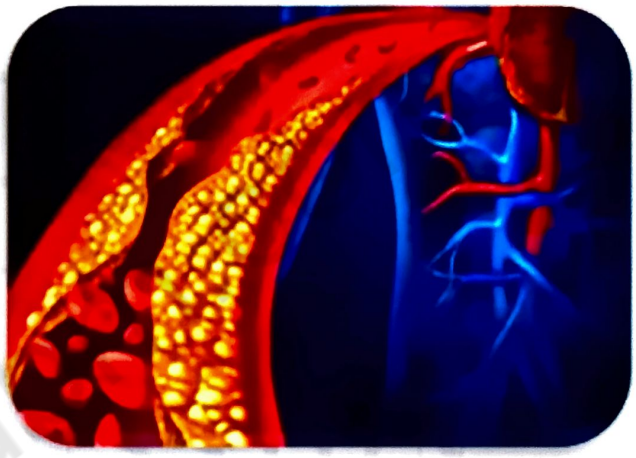
❖ Side effect

i. **Diarrhoea**

ii. **Abdominal pain**

iii. **Nausea**

iv. **Dyslipidaemias**



viii. Darunavir

- **Darunavir** is a potent newer PI **active against both HIV-1 and HIV-2,** including several strains resistant to other PIs.

❖ Pharmacokinetics

- First pass metabolism as well as systemic clearance by inhibiting CYP3A4.
- It is metabolized extensively by **CYP3A4** and **excreted in urine** with a **t½ of 15 hrs.**

❖ Side effect

- **Diarrhoea**
- **Rise in hepatic enzymes**
- **Rashes**
- **Allergic reactions**

4. Entry (fusion) inhibitor

i. Enfuvirtide (T-20)

This HIV-derived synthetic **peptide acts by binding to HIV-1** envelope **transmembrane glycoprotein (gp41)** which is involved in **fusion of viral and cellular membranes.**

❖ Mechanism of action

- Enfuvirtide **binds to a glycoprotein** on the virus and **inhibits the binding of the virus to the host cell membrane**, and there by **blocks the entry of the virus into the cell (fusion inhibitor)** thus **prevents transmission of HIV.**
- Fusion of the two membranes is thus **prevented and entry of the virus into the cell is blocked.**
- It is **not active against HIV-2.**
- No cross resistance with other classes of ARV drugs occurs.

❖ Pharmacokinetics

- **Administered S.C. Twice daily.**
- Enfuvirtide is given subcutaneously twice daily;
- Metabolism is by **hydrolysis** and microsomal enzymes are **not involved.**
- It can cause **local injection site** reactions

❖ Side effect

i. **Pneumonia**

ii. **Lymphadenopathy**

- Enfuvirtide requires **parenteral administration**— therefore, used only as an **add-on drug twice daily in patients not responding to other antiretroviral** drugs in **HIV-1 infected patients**

5. CCR-5 receptor inhibitor

i.Maraviroc

❖ Mechanism of action

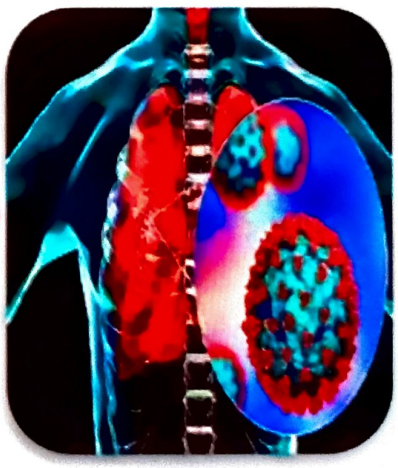
- **Maraviroc** CCR5 is coreceptor involved in fusion and entry of the virus into the CD4 cells.
- Maraviroc selectively **binds to CCR5 receptors** and **blocks the entry of HIV into the cells.**

❖ Pharmacokinetics

- It is effective **orally**
- Metabolized by **hepatic microsomal enzymes CYP3A4**
- Microsomal **enzyme inducers and inhibitors** can alter the **plasma levels of Maraviroc.**

❖ Side effect :-

i. Diarrhoea
ii. Sleep disturbances
iii. Cough
iv. Myalgia
v. Arthralgia
vi. Respiratory infections
vii. Raised liver enzymes



❖ Uses

i. Maraviroc is indicated in **HIV-1** infection not responding to other drugs.
ii. Maraviroc is in a class of medications called **HIV entry and fusion inhibitors**
iii. It works by **decreasing the amount of HIV in the blood**

6. Integrase inhibitor

Raltegravir , Dolutegravir (DTG)

i. Raltegravir

Integrase is a viral enzyme necessary for viral replication in both HIV- 1 and HIV-2 viruses.

❖ Mechanism of action

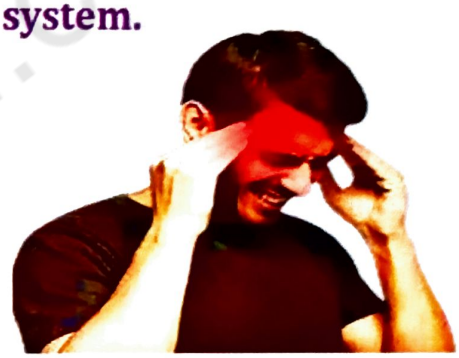
- Raltegravir, **elvitegravir** and dolutegravir **bind to integrase and prevent integration of HIV—DNA into the chromosomes of host cells.**

❖ Pharmacokinetics

- Raltegravir is effective on **oral administration**
- Metabolised in the **liver** but **not by CYP450 system.**

❖ Side effect :-

- **Nausea ,Diarrhoea**
- **Headache**
- **Dizziness**



ii. Dolutegravir (DTG)

Prevents integration of viral DNA into the host chromosome.

❖ Advantages

i. DTG is highly effective in **HIV-1 and HIV-2**

ii. Well tolerated

iii. Effective in **HIV resistant to other drugs.**

iv. Convenient to **use (once daily)**

v. Drug interactions are low

❖ Adverse Reactions

i. **Hypersensitivity reactions**

ii. **Raised serum creatinine.**

❑ Treatment of HIV Infection

- The treatment of HIV infection and its complications is complex, prolonged, needs expertise, strong motivation and commitment of the patient, resources and is expensive
- **Antiretroviral therapy (ART) is only 25 years old**, and is still evolving.
- Initially, **anti-HIV drugs** were used singly one after the other as each failed in a patient due to emergence of resistance.
- Understanding the biology of HIV infection: **'highly active antiretroviral therapy' (HAART)** with combination of 3 or more drugs.

➢ HIV Treatment principles and Guidelines

- **Initiating antiretroviral therapy**
- **Therapeutic regimens (HAART)**
- **Prophylaxis of HIV infection**
  - ✓ **Post-exposure prophylaxis (PEP)**
  - ✓ **Prophylaxis after sexual exposure**
  - ✓ **Perinatal HIV prophylaxis (First line regimen for pregnant women: Zidovudine + Lamivudine + Nevirapine)**

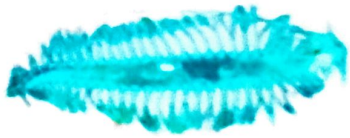
ANTHELMINTIC DRUGS

Points to be covered in this topic

1. INTRODUCTION OF ANTHELMINTICS
2. CLASSIFICATION OF ANTHELMINTICS DRUGS
3. MOA,PHARMACOKINETICS ,ADR,USES OF DIFFERENT CLASS OF DRUGS
4. RESISTANCE OF ANTHELMINTICS DRUGS

❑ INTRODUCTION

- Anthelmintic is the term used to describe **a drug used to treat infections of animals with parasitic worms.**
- This includes both flat worms, e.g., **flukes (trematodes)** and **tapeworms (cestodes)** as well as **round worms (nematodes).**
- The parasites are of huge importance for **human tropical medicine** and for **veterinary medicine.**
- Humans are **primary host for helminth infections,** in the sense that they harbour the sexually mature form that reproduces.
- **Eggs or larvae then pass out of the body** and infect the **secondary (intermediate) host.**
- They harm the host by depriving him of **food, causing blood loss, injury to organs, intestinal or lymphatic obstruction** and by secreting toxins.



➢ Anthelmintics drugs are two types

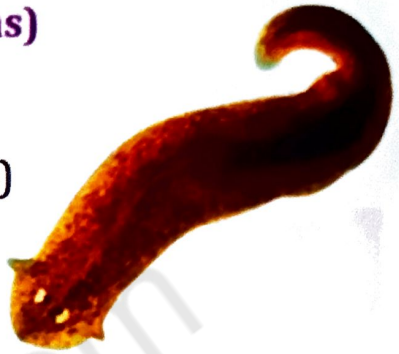
a) Vermicide (kill worms)

b) Vermifuge (expel the worms) infesting helminths.

❖ Classification on helminths

The helminths comprise two major Groups:

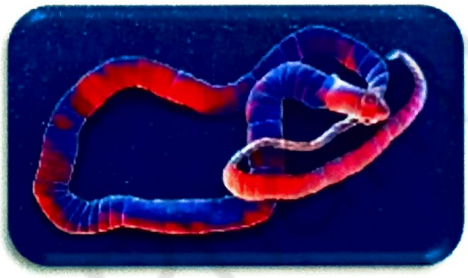
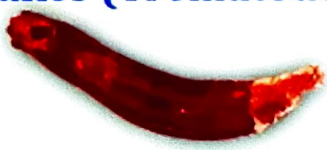
1. Nemathelminths (Nematodes - roundworms)
2. Platyhelminths (Flatworms)



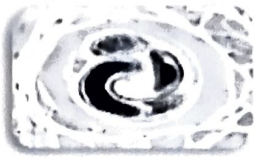
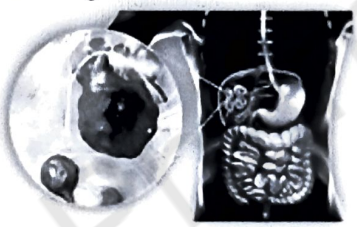
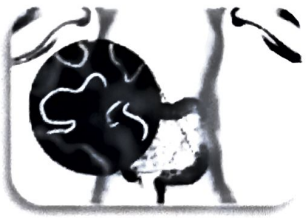
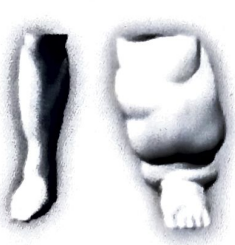
The latter group is subdivided into the two groups)

a) Trematode (Flukes)

b) Cestodes (Tapeworms)

CLASS	MICROORGANISM
Tapeworms (cestodes) 	Taenia solium, Taenia saginata, Hymenolepis nana, Echinoccocus granulosus
Flukes (Trematodes) 	Schistosoma, Fasciola hepatica
Roundworms (Nematodes) 	Ascaris, Onchocerca, Trichuris, Neactoramericanus, Anchylostoma duodenale

❑ CLASSIFICATION ON ANTHELMINTICS DRUGS

MICRORGANISM	DRUGS
For Roundworm, Hookworm, Pinworm 	Albendazole , Mebendazole, Pyrantel pamoate, Piperazine, Levamisole
For Whipworm, Trichinella spiralis 	Albendazole ,Mebendazole
For Tapeworms 	Praziquantel , Niclosamide ,Albendazole
For Hydatid Disease 	Albendazole, Mebendazole
For Threadworm 	Ivermectin , Albendazole
For Filariasis  	Diethylcarbamazine , Ivermectin, Albendazole

❖ CHOICE OF DRUGS FOR HELMINTHIASIS

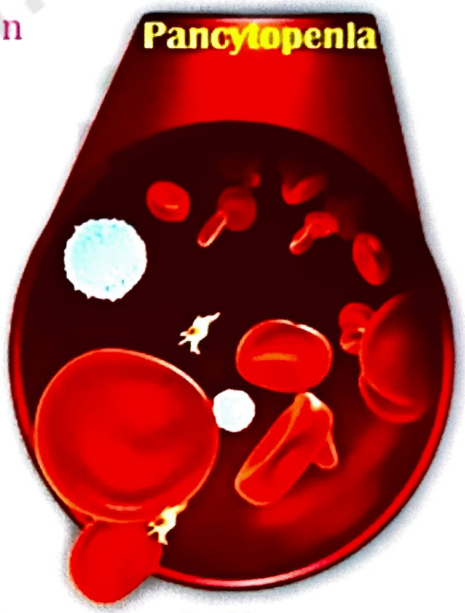
Worm	First choice drugs	Alternative drugs
1. ROUNDWORM		
Ascaris lumbricoides	Mebendazole, Albendazole, Pyrantel	Piperazine, Levamisole Ivermectin
2. HOOKWORM		
Ancylostoma duodenale	Pyrantel, Mebendazole, Albendazole	Levamisole
Necator americanus	Mebendazole, Albendazole	Pyrantel
3. PIN WORM		
Enterobius (Oxyuris) vermicularis	Pyrantel, Mebendazole, Albendazole	Piperazine
4. THREAD WORM		
Strongyloides stercoralis	Ivermectin	Albendazole
5. WHIPWORM		
Trichuris trichiura	Mebendazole	Albendazole
6. Trichinella spiralis	Albendazole	Mebendazole
7. FILARIA		
Wuchereria bancrofti, Brugia malayi	Diethyl carbamazine, Ivermectin	Albendazole
8. CUTANEOUS LARVA MIGRANS		
Ancylostoma caninum	Albendazole	Ivermectin
9. TAPEWORMS		
Taenia saginata	Praziquantel	Niclosamide, Albendazole
Taenia solium	Praziquantel	Niclosamide, Albendazole
Hymenolepis nana	Praziquantel	Niclosamide, Nitazoxanide
Neurocysticercosis	Albendazole	Praziquantel
10. HYDATID DISEASE		
Echinococcus granulosus,	Albendazole	Mebendazole
E. multilocularis	Albendazole	

i. Albendazole

- Albendazole, a **broad-spectrum oral anthelmintic agent**.
- It is the drug of choice for treatment of **hydatid disease** and **cysticercosis.**
- It is also used in the treatment of **pinworm and hookworm, round worm, whip worm,** and **thread worm infections.**
- One dose treatment is effective against **round worm, pin worm** and **hook worm infections** which are comparable to 3 days treatment with mebendazole.
- Three days treatment is necessary for tapeworms including **H. nana.**
- It has **weak microfilaricidal action**.

❖ Mechanism of action (Albendazole , Mebendazole ,Thiabendazole)

- Drugs inhibiting polymerization of β – tubulin



❖ Pharmacokinetics

- Albendazole is erratically **absorbed after oral administration**, but absorption is enhanced by a high-fat meal.
- It i is **metabolized in liver**
- **Excreted in urine & T½ 8.5 hours**

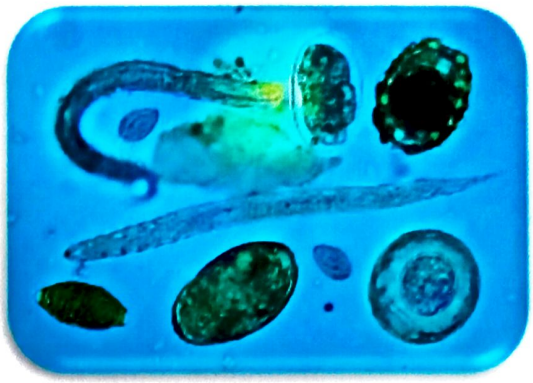
❖ Adverse effects

i. **Mild and transient epigastric distress**
ii. **Diarrhea**
iii. **Headache**
iv. **Nausea**
v. **Dizziness**
vi. **Increases in liver enzymes**
vii. **Pancytopenia**
viii. **Embryotoxicity in animals**
ix. **Pregnant women is contraindicated**
x. **Lassitude, and insomnia ,fatigue, alopecia**

❖ Uses

✓ It is also used for

- ***Ascaris*, hookworm, *Enterobius* and *Trichuris***
- **Tapeworms and *Strongyloides***
- **Trichinosis**
- **Neurocysticercosis**
- **Hydatid disease, Filariasis**



ii. Mebendazole

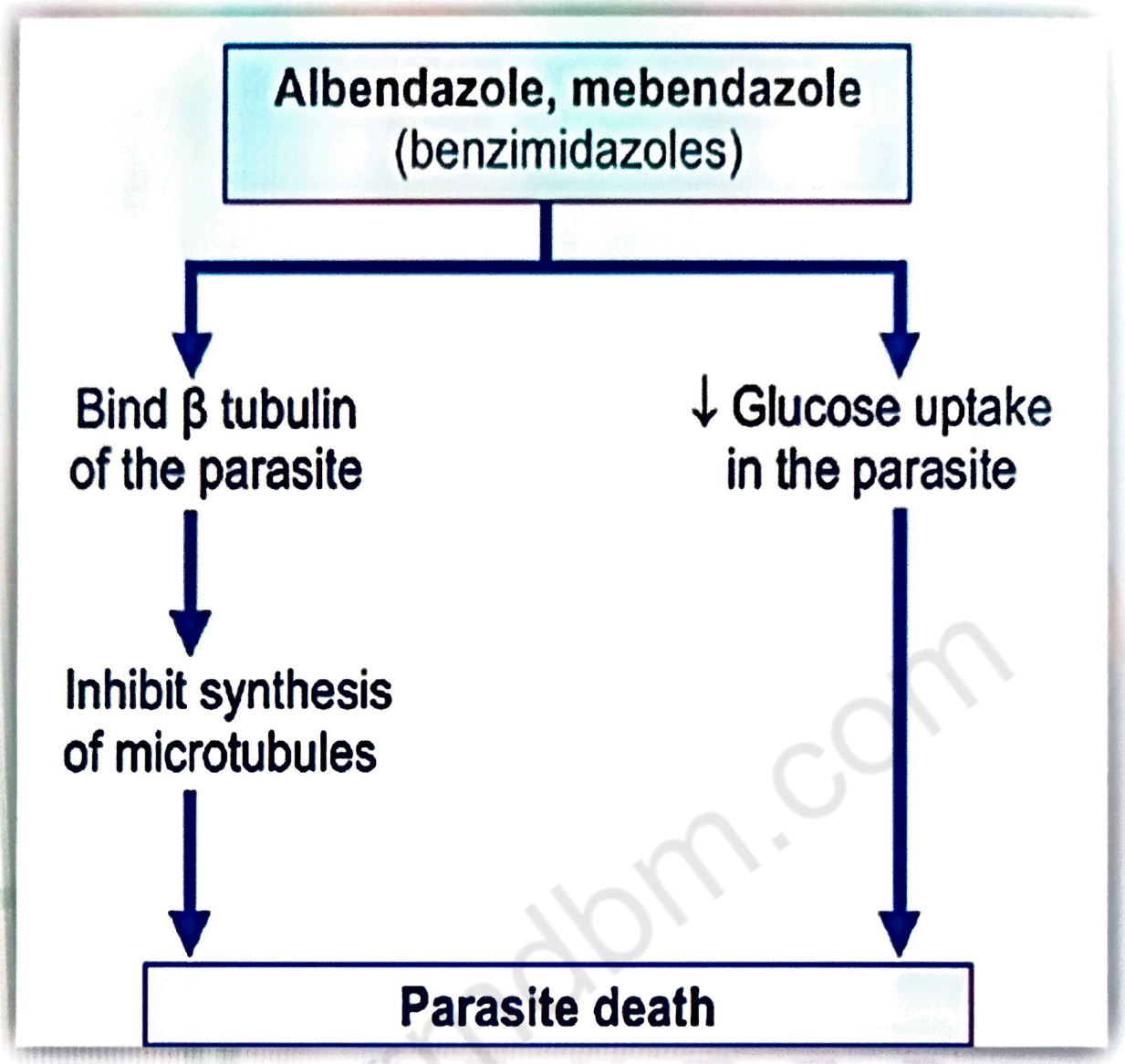
- It is a **benzimidazole** introduced in **1972.**
- Mebendazole has produced nearly **100% cure rate/reduction in egg** count in **roundworm, hook worm** (both species), **Enterobius** and **Trichuris** infestations, but is much less active on ***Strongyloides.***

❖ Mechanism of action (Albendazole , Mebendazole ,Thiabendazole)

- Mebendazole appears to be the **microtubular protein 'β-tubulin'** of the parasite.
- It **binds to β-tubulin** of susceptible worms with **high affinity** and **inhibits its polymerization.**
- **Intracellular microtubules in the cells of the worm** are gradually lost
- **It blocks glucose uptake in the parasite**, inhibits some mitochondrial enzymes and depletes its glycogen stores.
- **Hatching of nematode eggs** and their **larvae are also inhibited.**
- **Ascaris ova are killed.**

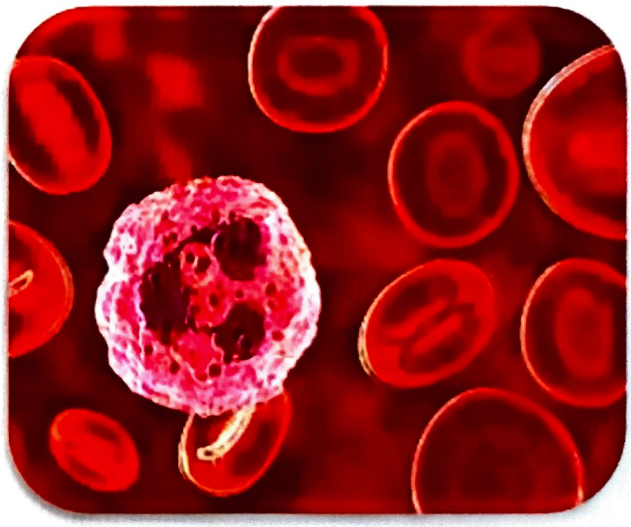
❖ Pharmacokinetics

- **Absorption of mebendazole from intestines** is minimal; **75–90%** of an **oral dose is passed in the faeces.**
- Metabolites in **urine/faeces.**



❖ Adverse effects

- Diarrhoea
- Nausea and abdominal pain.
- Allergic reactions
- Loss of hair and granulocytopenia



Dose :- 100 mg chewable tablet

100 mg/5ml suspension

100 mg tablet

❖ Uses

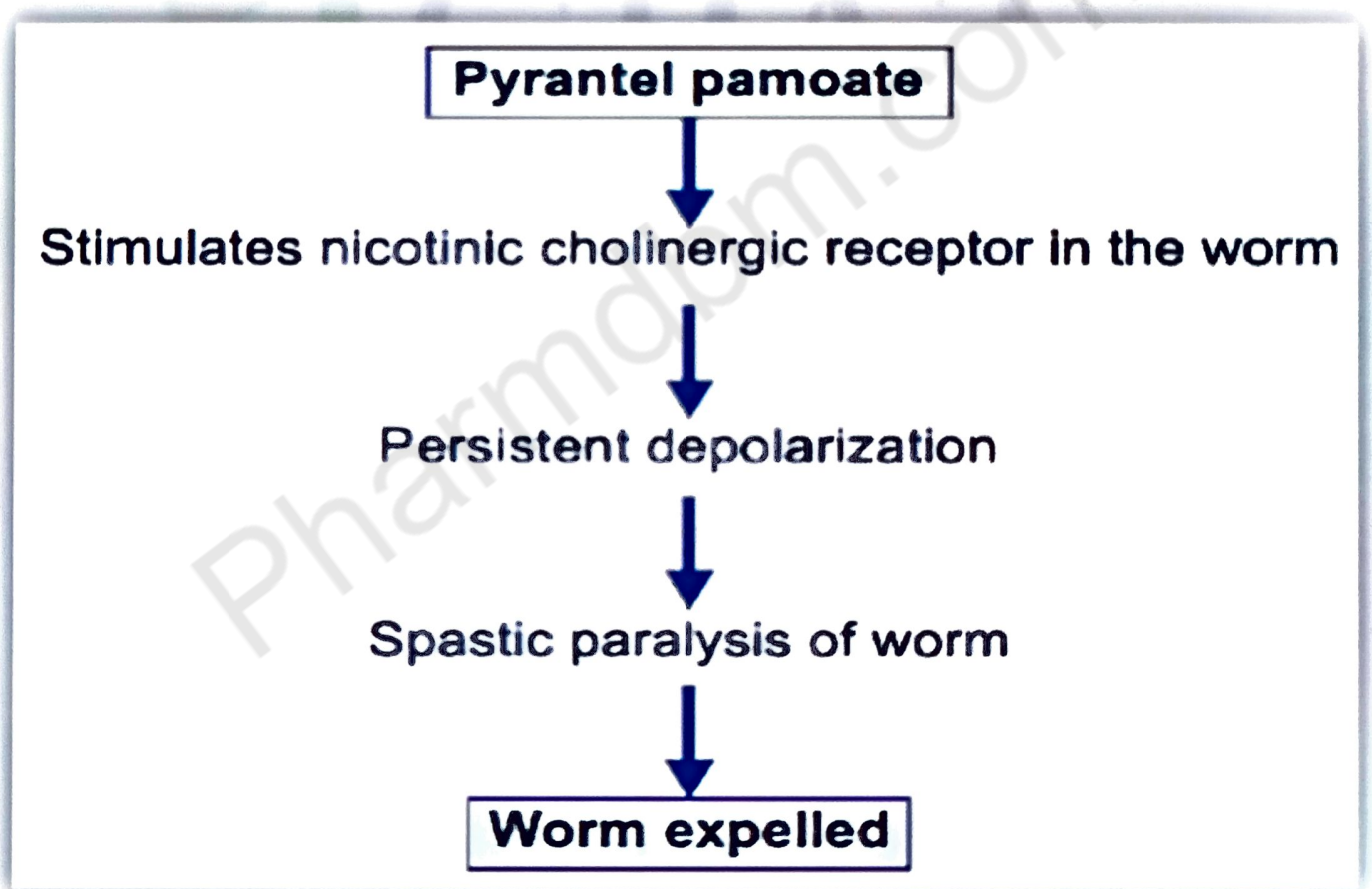
- It is a drug of choice in the treatment of infections by **whipworm eggs, pinworm , hookworms ,** and **roundworm.**

iii. Pyrantel pamoate

- It was introduced in **1969** for **pin worm** infestation in children use **roundworm** and **hookworm** .
- Efficacy against **Ascaris, Enterobius** and **Ancylostoma**.
- It is **less active against Strongyloides** and **inactive against *Trichuris***

❖ Mechanism of action

- **Drugs causing spastic paralysis by stimulating N_N receptor**
- **Activation of nicotininic cholinergic receptors**
- **Persistent depolarization leading to contracture and spastic paralysis**
- **Expelling of worms- inhibition of acetylcholinesterase**



❖ Pharmacokinetics

- Only **10–15% of an oral dose** of **pyrantel pamoate is absorbed.**
- This is partly **metabolized** and **excreted in urine**

❖ Adverse effect

- **Mild GIT disturbance , Headache , Dizziness and drowsiness**

❖ Uses

Originally for thread worms but extended to round worms and hook worms as well- Less active against necater and strongyoides- Inactive against Trichuris .

iv. Praziquantel

This anthelmintic has wide ranging activity against *Schistosomes*, other trematodes, cestodes and their larval forms but not nematodes

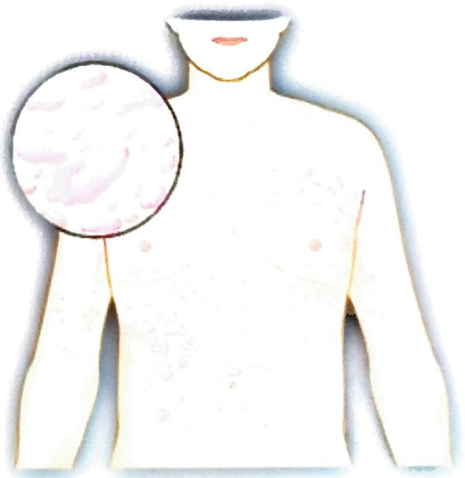
❖ Mechanism of action

- Drugs causing influx of calcium
- Rapidly taken up by worms
- Leakage of intracellular Ca++ causing paralysis
- Worms lose grip on intestinal wall including tissues and veins
- Acts against all stages of worms including larvae

✓ Other MOA-vacuolization of membrane and release of contents of tapeworms

❖ Pharmacokinetics

- Praziquantel is rapidly absorbed from intestines.
- High first pass metabolism in liver limits its systemic bioavailability.
- It crosses blood-brain barrier and attains therapeutic concentrations in the brain and CSF.
- The plasma t½ is short (1.5 hours).
- Metabolites are excreted in urine.



❖ Adverse effects

- Diarrhoea, Nausea and abdominal pain
- Allergic reactions
- Dizziness and malaise. ,Itching, urticaria, rashes, fever & bodyache

❖ Uses

i. **Tapeworms**

ii. **Neurocysticercosis**

iii. **Schistosomes**

v. Niclosamide

Niclosamide is a **highly effective drug against cestodes** infesting **man—*Taenia saginata, T. solium, Diphyllobothrium latum*** and ***Hymenolepis nana***, as well as **pin worm *(Enterobius)*,**

❖ Mechanism of action

- **Inhibition of oxidative phosphorylation in mitochondria and interference of anaerobic generation of ATP.**

❖ Pharmacokinetics

- Niclosamide is **tasteless** and **nonirritating.**
- It is minimally absorbed from **G.I.T.**—no systemic toxicity occurs.

❖ Adverse effects

- **Malaise, pruritus** and **light headedness** are rare.
- Niclosamide is **safe during pregnancy** and in **poor health patients**

❖ Uses

- **Against tape worms - saginata, solium, latum and nana**

vi. Ivermectin

- Ivermectin is a **semisynthetic analog of avermectin B** obtained from ***Streptomyces avermitilis.***
- Ivermectin is effective against many **nematodes, arthropods** and **filariae** that **infect animals and human beings.**

- Ivermectin is very effective against the **microfilaria of Onchocerca volvulus.**

❖ Mechanism of action

- Ivermectin **acts by paralysing the worms** by **binding to glutamate-gated chloride channels** and also enhancing GABA activity.
- It binds to the channels and enhances the permeability of the cell membranes to **chloride ions leading to hyperpolarization and paralysis.**
- It also enhances the **GABAergic transmission** in the nerves of the nematodes.

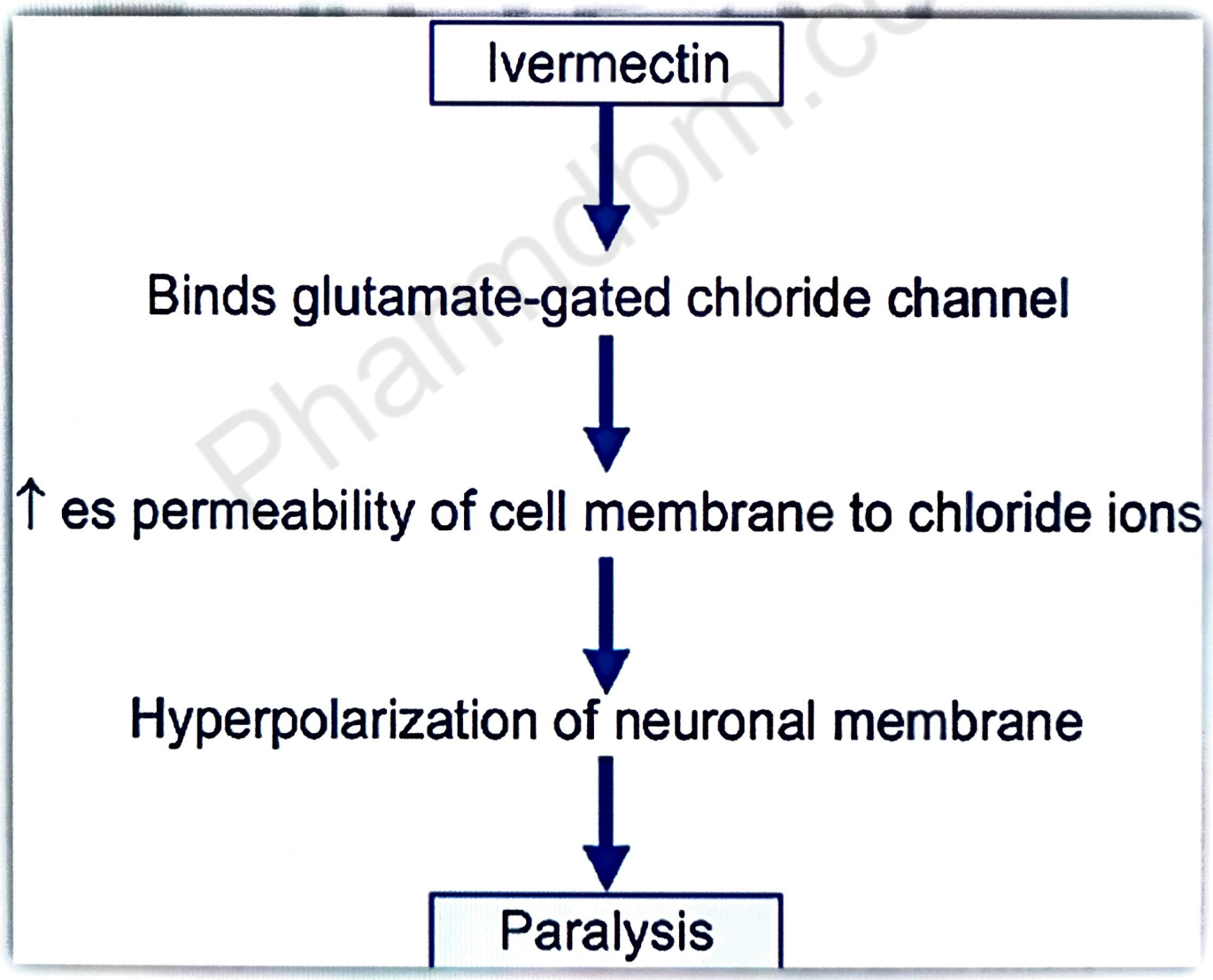


Fig :- Mechanism of action of Ivermectin

❖ Pharmacokinetics

- Ivermectin is **well absorbed orally**
- Distributed in the body, but **does not enter CNS**.
- It is **metabolized by CYP3A4**

❖ Adverse Effects

- **Nausea and vomiting**
- Allergic reactions can result due to **hypersensitivity** to the dying **microfilarial proteins (mazzotti reaction).**
- Pruritus
- Urticaria, myalgia

❖ Uses

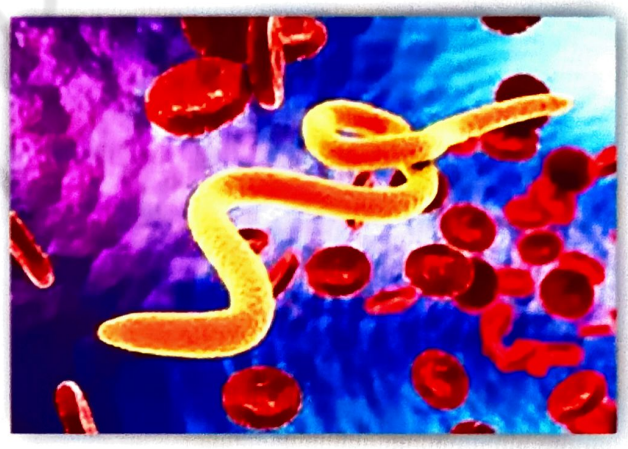
i. Ivermectin is the only drug effective orally in **scabies and pediculosis**

ii. **Onchocerciasis**

iii. **Lymphatic filariasis**

iv. **Strongyloidiasis**

v. **Covid-19**



vii. Diethylcarbamazine

Developed in **1948,** it is the first drug for **filariasis caused by the nematodes**

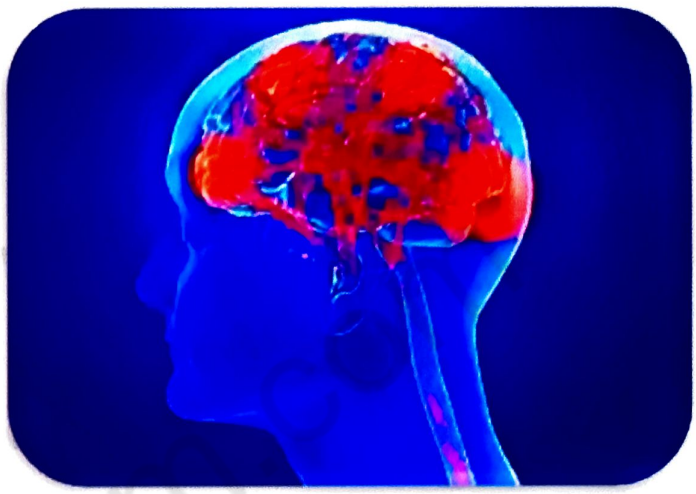
❖ Mechanism of action

- Drugs altering **microfilarial membrane** and **increasing phagocytosis.**
- Alteration of MF membrane - to be readily **phagocytosed by tissue monocytes**
- Since **piperazine derivative** - **hyperpolarization** and **muscle weakness**

❖ Pharmacokinetics

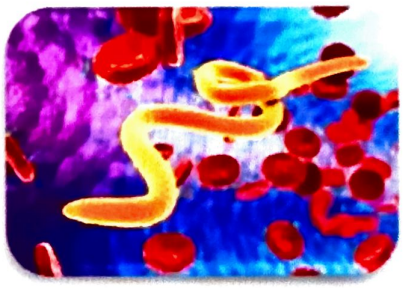
- Diethylcarbamazine is **microfilaricidal**
- DEC is absorbed after **oral ingestion**,
- **Distributed all over the body (V = 3–5 L/kg)**
- **Metabolized in liver and excreted in urine.**
- Excretion is **faster in acidic urine.**

❖ Adverse effects



- **Nausea**
- **Anorexia**
- **Lethargy**
- **Febrile reaction**
- **Renal haemorrhage**
- **Encephalopathy**
- **Leukocytosis** and **mild albuminuria**

❖ Uses



- **Filariasis**
- **Tropical eosinophilia**

viii. Piperazine

- Introduced in 1950
- It is a highly active drug **against *Ascaris* and *Enterobius***

❖ Mechanism of action

- Drugs causing flaccid paralysis by **$GABA_A$, agonistic action.**
- It is also a **GABA receptor agonist.**
- **Hyperpolarization of Ascaris muscles GABA agonistic action of Cl channel opening**
- Decreased responsiveness to Ach contractile response – **flaccid paralysis**

❖ Pharmacokinetics

- Oral dose of piperazine is **absorbed.**
- Metabolized in **liver**
- Excreted in **urine.**

❖ Adverse effects

- **Nausea**
- **Vomiting**
- **Abdominal discomfort**
- **Urticaria**
- **Nephrotoxicity**

❖ Uses

- Used for treatment of **Ascaris** and **Enterobios**
- Piperazine citrate is indicated for **roundworm infestation.**
- It is also **safe in pregnancy.**

❖ Contra-indications

- **Renal insufficiency**
- **Epileptics**

viii. Levamisole & Tetramisole

- Tetramisole was developed in the late **1960s.**
- It is **racemic** , its **levo isomer (levamisole)** was found to be more active and preferable.
- Both are active against many nematodes, but use is restricted to **ascariasis** and **ancylostomiasis** as a second line drug.
- It is also an **immunomodulator.**

❖ Mechanism of action

- **Drugs causing tonic paralysis by stimulating ganglia**

❖ Adverse effects

- **Abdominal pain**
- **Giddiness**
- **Fatigue**
- **Drowsiness** or **insomnia is low**

❖ Uses

Levamisole is effective against **roundworms** and **hookworms** and can be used as an alternative drug in these infestations.

Dose

- ✓ **Ascariasis —Single dose 150 for adults, 100 mg for children 20–39 kg body weight, 50 mg for 10–19 kg.**
- ✓ **Ancylostomiasis —Two doses at 12 hour intervals. It is less effective against Neccator**

❑ RESISTANCE TO ANTHELMINTIC DRUGS

- ✓ Efflux of the drug by **P-glycoprotein transporter**.
- ✓ **Reduced affinity for binding of drug** as in **benzimidazoles** to the **beta tubulin.**
- ✓ Modification of the structure of the binding site.