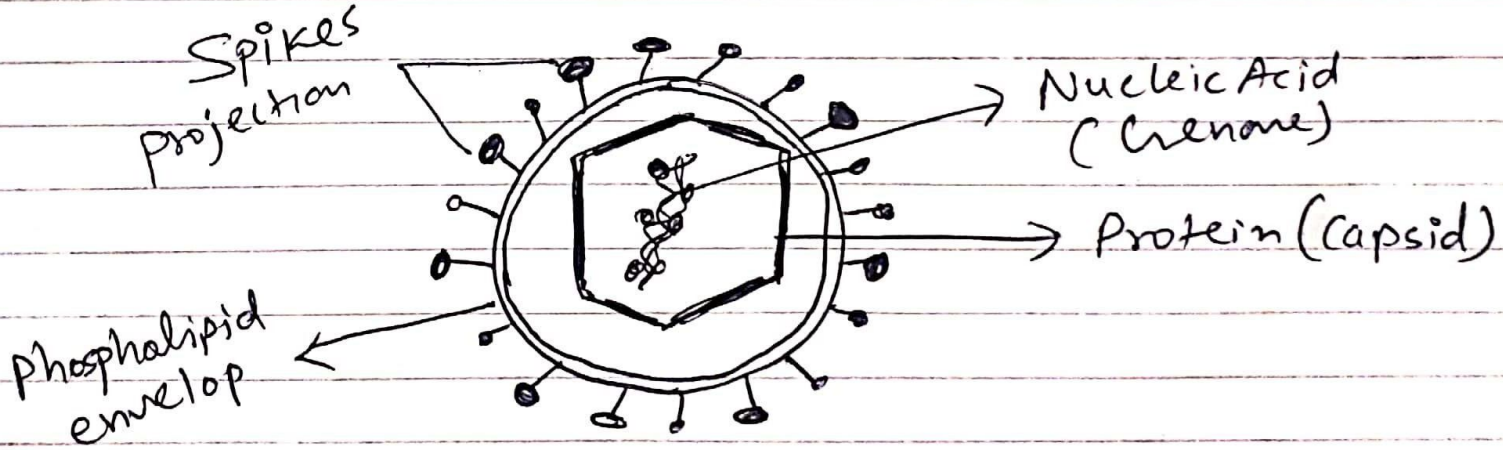
Antiviral Agents

Virus :- They can be simply defined viral particles consist of single nucleic acid either RNA or DNA encoding viral genome & surrounded by a protein coat.

They are obligate intracellular parasite and capable of replication only in host cell- i.e. such as bacterial, animal & plant cells.



Typical enveloped virus structure

Capsid :- protective protein coat in different shape in different types of virus. They cover genome. They help virus to survive in different environment & have function in receptor recognition & targetting succeptible host.

Phospholipid envelop:- Some virus have phospholipid envelope which is derived from host cell membrane. They surround the capsid. from this envelop, spike protein protruded to out side called spike projection. which are chemically glycoprotein.

The function of spike projection to recognise the host & bind only at certain site of host body.

for example in Influenza virus two types of spike projection (glycoprotein) found like Neuraminidase (N)
Haemagglutinin (H)

That why nomenclature of Influenza virus based on different form of H & N. ex H^1N^1, H^5N^5 etc.

So antiviral agents are drug or molecules which are against the viral infections.

Ex Specific antiviral
Antiherpes Agent
Anti HIV agent
Anti influenza agent

Classification of Antiviral Agents

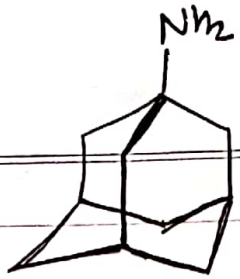
Antiviral agents do not destroy their target but they inhibit their development (replication inside host).

Classification based on therapeutic uses:-

- Antiherpes virus agents
  - Ex → Acylovir, famcylovir
  - → Idoxuridine,
  - Foscarnet
  - → Trifluoridine
  - → Valacyclovir
  - Ganeyclovir
- Anti influenza agents
  - → Amantadine
  - → Oseltamivir
  - → Peramivir
  - → Rimantadine
  - → Zanamivir
- Other Antiviral
  - → fomivirsen
  - → Ribavirin
  - → Interferon
  - → ~~Fomiv~~. Enfuvirtide
  - → Viramidine
- Antiretroviral Agents
  - Nucleoside reverse transcriptase Inhibitor (NRTIs)
    - Ex → Zidovudine
    - → Didanosine
    - → Stavudine
    - → Zalcitabine
    - → Lamuvudine
  - Non Nucleoside reverse transcriptase Inhibitors (NNRTIs)
    - → Efavirenz
    - → Nevirapine
    - → Delavirdine
    - → Loviride
  - Protease Inhibitors (Navir family)
    - → Sequinavir
    - → Indinavir
    - → Ritonavir
    - → Nelfinavir
    - → Liponavir

Amantadine:-

HCl salt



Adult dose
100mg / BD

→ It is Carbocyclic (fused) amine

→ Used as antiviral agents against Influenza-A virus, (Not Influenza-B)

⇒ Also used ~~in Parkinson~~ as antiparkinsonian drug.

Mode of Action:-

⇒ Interferes with release of infectious viral nucleic Acid in ~~host~~ host cell via interaction of trans membrane domain of M2 protein of virus

⇒ In some cases it also prevents virus assembly during replication in host cell.

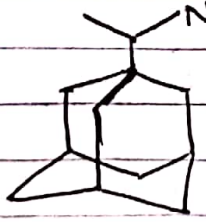
Rimantadine:-

HCl salt

4-5 time more active than amantadine

⇒ It is structural analog of amantadine

⇒ It Can Shorten the duration & ~~Se~~ Change the severity of influenza-A virus.



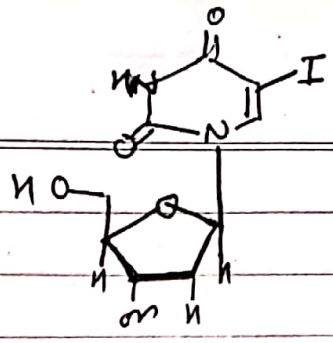
MOA Similar to amantadine (Inhibition of viral entry into cell)

⇒ Bind to specific cell surface receptor & inhibit viral penetration

⇒ Prevent uncoating of virus protective shells (Capsid & envelop)

⇒ Also have antiparkinsonian property partially due to NMDA antagonism.

Idoxuridine :



(Against Herpes simplex virus (HSV))

⇒ Act as anti herpes virus agent

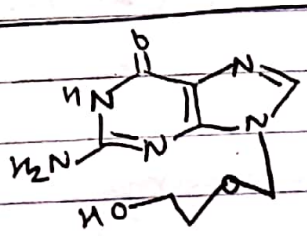
⇒ It is a nucleoside analog of (deoxyuridine)

MOA ⇒ Due to structural analog of deoxyuridine, the drug incorporate itself in the replication of viral genome (DNA synthesis).

⇒ So faulty synthesis of DNA which is not having virulence i.e. unable to infect & destroy the host cell.

⇒ The bulky Iodine atom blocks base pairing with other nucleotides

Acyclovir :



⇒ Primarily used for treatment of Herpes simplex virus infection. (HSV), Chickenpox

⇒ Also used as prophylaxic treatment against Cytomegalovirus after transplant

⇒ Serious side effect : kidney problem, low platelets

⇒

MOA :- Acyclovir is structural analog of guanosine nucleoside

Acyclovir —(Viral thymidine kinase)→ Acyclovir monophosphate —(Host kinase)→ Acyclovir triphosphate

Acyclovir triphosphate → Competatively inhibit & inactivate Viral DNA polymerase → Preventing further Viral DNA synthesis

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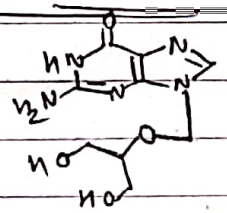
Ganciclovir :-

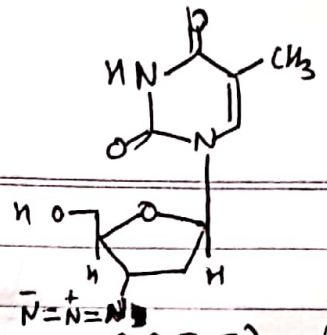


⇒ Active against CMV & Herpes simplex viral infection (HSV)

⇒ MOA :- Similar to acyclovir (nucleoside analog of 2-deoxy guanosine)

⇒ Both host & viral mechanism used for activation of drug against viral multiplication.

⇒ Ganciclovir triphosphate serve as poor substrate for chain elongation & disrupting viral DNA synthesis.



Thymidine analog

Zidovudine: (ZDV)

⇒ Also called azidothymidine (AZT) & comes under antiretroviral medication

⇒ retro virus :- Have capability to synthesize viral DNA from viral RNA using RNA dependent DNA polymerase enzyme.

⇒ Drug mainly used to ~~prevent~~ HIV infection

⇒ Used with other antiretroviral agents

⇒ Used by oral & IV route

MoA :- Act as NRTIs (Nucleoside Reverse Transcriptase Inhibitor)

⇒ It inhibit HIV viral reverse transcriptase enzyme

↓

Inhibit viral DNA synthesis from viral RNA

↓

↓ replication of virus

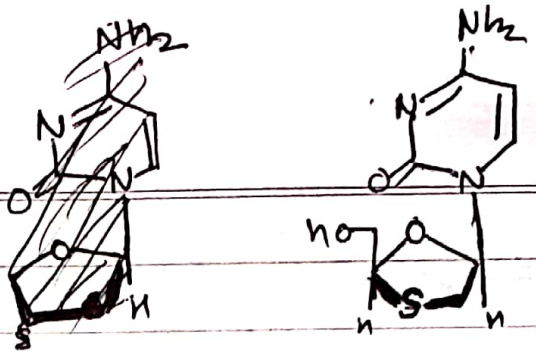
⇒ Reverse transcription is necessary for production of HIV's Double Strand DNA which further integrated to human cell DNA for survival

⇒ At high dose, the side effect is due to inhibition of cellular (Host) DNA polymerase enzyme.

⇒ Generaly used in Combination with lamivudine and or abacavir

Lamivudine :-

Used in HIV/AIDS



⇒ It is also a nucleoside reverse transpriptase inhibitor (NRTIs)

⇒ Usually given in combination with Zidovudine/Abaca to reduce resistant to HIV infection

MOA : It is nucleoside analog of cytidine.

⇒ It is converted to active metabolite by phosphorylation.

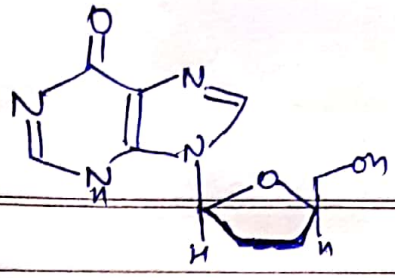
⇒ The phosphorylated lamivudine analog compete for incorporation into viral DNA

⇒ It inhibit both Type-I & Type-II HIV reverse transcriptase enzyme.

⇒ Also inhibit Hepatitis-B Virus reverse transcriptase & polymerase

⇒ Due to lack of 3'-OH group in 5 member sugar molecule type ring, It block the chain elongation of DNA & growth of DNA is stoped.

Didanosine :=>



⇒ The drug is active against HIV-1 infection

⇒ It is also a nucleoside analog of adenine

⇒ It is used in combination of other drug as a part of (HAART) therapy
(↓ Highly active antiretroviral therapy)

MOA :=> Basic Ring in the didanosine resembles hypoxanthine attached with sugar molecule

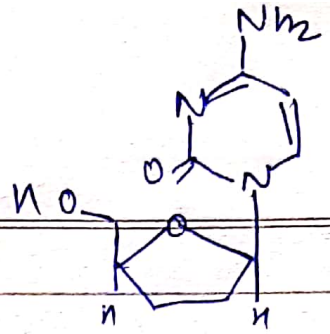
Didanosine —(Cellular Phosphorylation)→ di deoxy adenosine triphosphate

↓

Competative inhibitor of dATP ← Inhibition of Reverse Transcriptase (~~Reverse trans criptase~~)

⇒ It is also act as Chain terminator due to faulty synthesis of DNA

Zalcitabine



⇒ Basically it is dideoxycytidine & nucleoside analog reverse transcriptase inhibitor.

⇒ Third antiretroviral drug used against HIV/AIDS treatment.

⇒ Was Used in combination therapy against HIV infec.

⇒ Due to serious adverse effect (peripheral neuropathy), now it is discontinued in some countries.

MOA :- It is nucleoside analog of ~~pyrimidine~~

⇒ Deriva

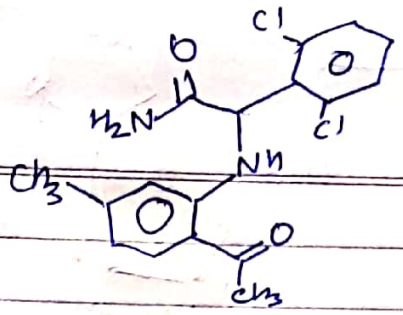
Zalcitabine —(Phosphorylated by Cel)→ active triphosphate

active triphosphate → Bind to reverse transcriptase & Inhibit it

Inhibit it → No DNA Chain elongation due to No hydroxy group at 3' position of sugar ring.

(NNRTIs)

(1) **Loviride** :-



⇒ It is non-nucleoside reverse transcriptase inhibitor (NNRTIs)

⇒ Active at IC_{50} of 0.3 µm against reverse transcriptase of HIV-1

⇒ It inhibit HIV-I, HIV-2 & SIV replication (Simian Immunodeficiency virus in nonhuman african primates) in MT-4 cells

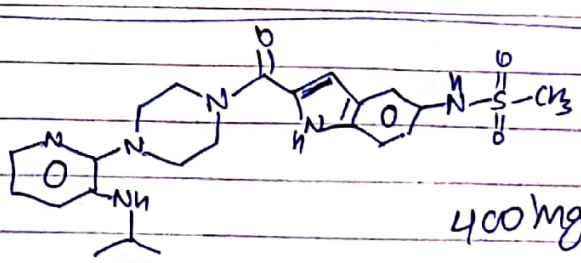
MOA :

⇒ Act as inhibitor of reverse transcriptase enzyme ~~at~~ at other binding site (called "pocket")

⇒ Loviride do not compete with nucleoside-RT analogs.

⇒ DNA chain elongation stop in HIV patient.

(2) **DELAVIRDINE**



400 mg / TDS

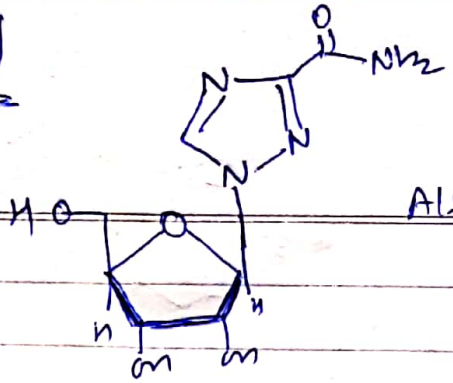
⇒ Non-nucleoside RTIs member

⇒ Bind directly to viral RTase & block RNA & DNA dependend DNA polymerase enzyme activity via disrupting enzyme catalytic site

⇒ Used as part of HAART therapy against HIV-1

Other Antiviral

Ribavirin



Also known as Tribavirin

⇒ Synthetic nucleoside analog (purine analog)

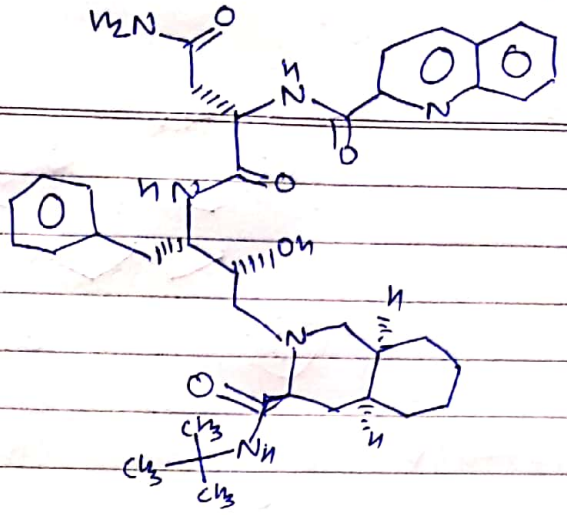
⇒ Uses to treat RSV (Respiratory syncytial virus) affect lower respiratory tract
Hepatitis-C &
Viral haemorrhagic fever

MOA It is a prodrug → metabolism → Active purine analog (phosphorylated) → Interfere with RNA metabolism Required for viral replication

IN RNA virus: It behave as adenine & guanine analog based on it's rotation → Incorporated in RNA Chain as an analog → Mutation in RNA dependent replication in RNA virus

In DNA virus: No effect so only ~~RNA~~ act as RNA nucleoside mimics

(1) Saquinavir



Antiretroviral drug

⇒ Used in combination with other drug such as ritonavir, ~~[illegible]~~ or lopinavir to increase it's effect

= Serious side effects — Heart burn
⇒ High blood lipids
liver problem

⇒ Comes under protease inhibitor class

MOA :-

⇒ Work as HIV protease inhibitor

⇒ This enzyme cleaves protein mol. into small fragment

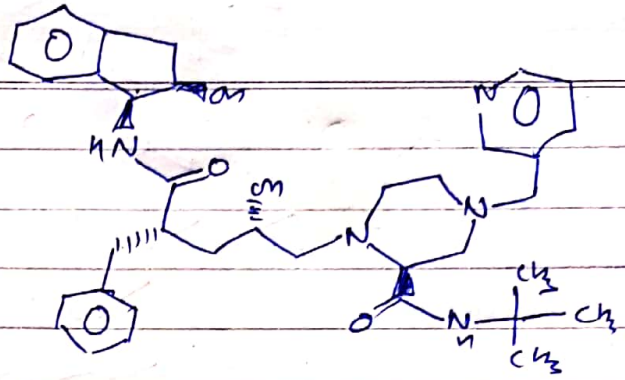
⇒ This enzyme is essential for — Viral replication within cell
↳ Release of viral particle from the host cell

Sequinavir → bind to active site of HIV protease
↓
prevent cleavage of polyprotein
↓
prevent maturation of vims

⇒ The drug inhibit HIV-protease of both the strain HIV-1 & HIV-2

Protease Inhibitor class

(2) Indinavir :⇒



⇒ It is another drug comes under protease inhibitor class.

⇒ Used as component of HAART therapy in HIV/AIDS

MOA :. Used as inhibitor of HIV protease enzyme

↓

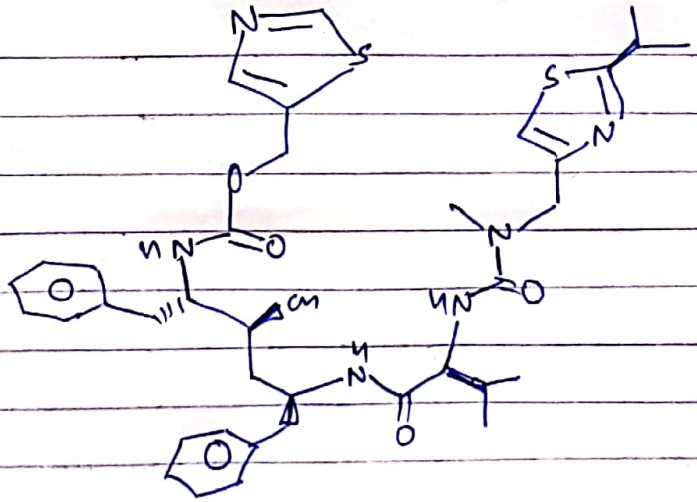
HIV cannot reproduce

↓

Low viral load for infection

(3) Ritonavir :⇒

protease inhibitor



MOA :- ⇒ originally developed as HIV protease inhibitors but now rarely used.

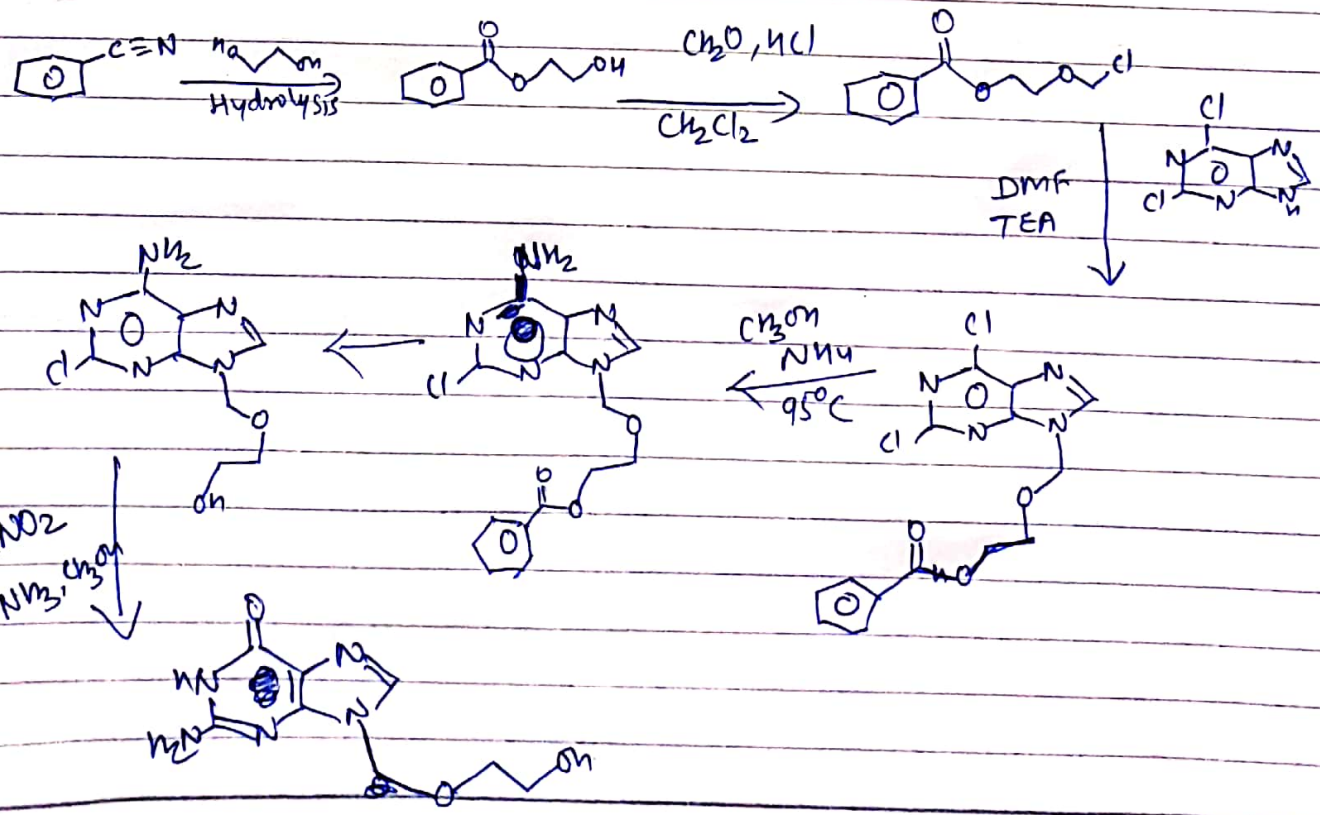
⇒ It is widely used as a booster of other protease inhibitor

⇒ It inhibit the metabolism of other protease inhibitor by liver, intestine & CYP3A4.

⇒ So level of other protease inhibitor ↑ & actively inhibit protease inhibitor

⇒ This mechanism drastically reduced the adverse reaction observed with HAART therapy

Synthesis – Acyclovir



Acyclovir

Scheme-2