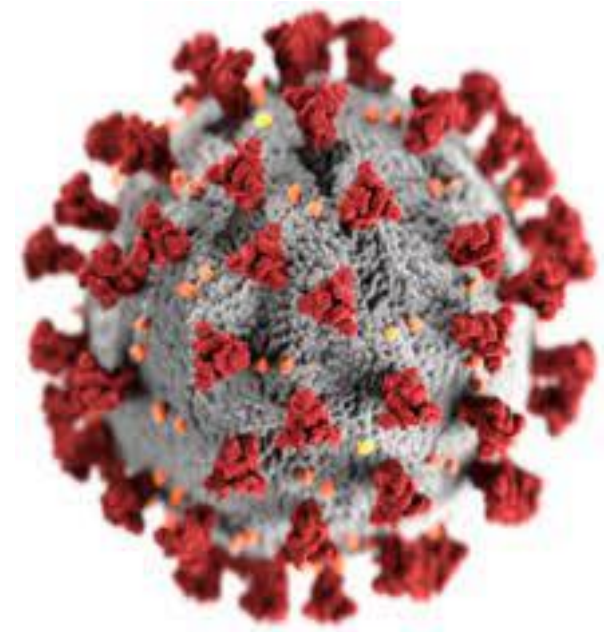


ANTIVIRAL DRUGS



BE SAFE WEAR A MASK

- Study of virus is called virology
- The *latin word virus means venom or poison.*
- Defined as sub microscopic entity consisting of a single nucleic acid surrounded by a protein coat and capable of replication only within the living cells of bacteria, animals or plants.



Difference Between Bacteria And Virus:

BACTERIA

- Living organism, unicellular, one cell
- Larger (1000nm)
- In latin means little sticks
- Usually treated with antibiotics

VIRUS:

Not living, no cells

- Smaller (20-300nm)
- In latin means poison
- Antibiotics will not effect the disease

Characteristics Of Viruses

- They cannot be observed using a light microscope
- They have no internal cellular structure
- They contain either DNA or RNA, but not both
- They are incapable of metabolism
- Viruses are smaller than bacteria
- They replicate only inside living cells.
- Viruses lack cellular organelles, such as mitochondria and ribosomes.

Difference Between DNA & RNA Virus

Double stranded

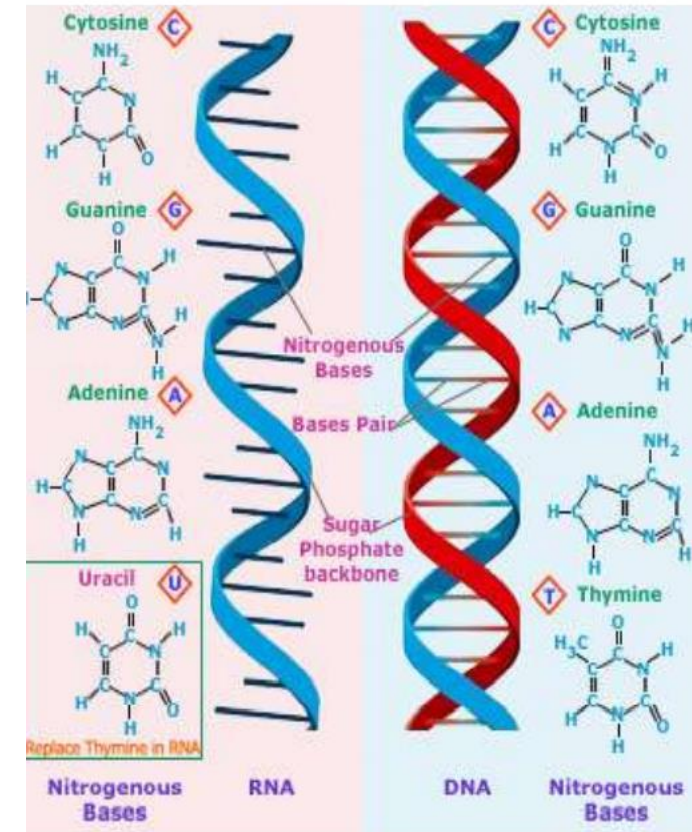
- Nitrogenous bases (Adenine, Cytosine, Guanine, & Thymine)
- Type of sugar : Deoxyribose
- Location: in Nucleus

• Single Stranded

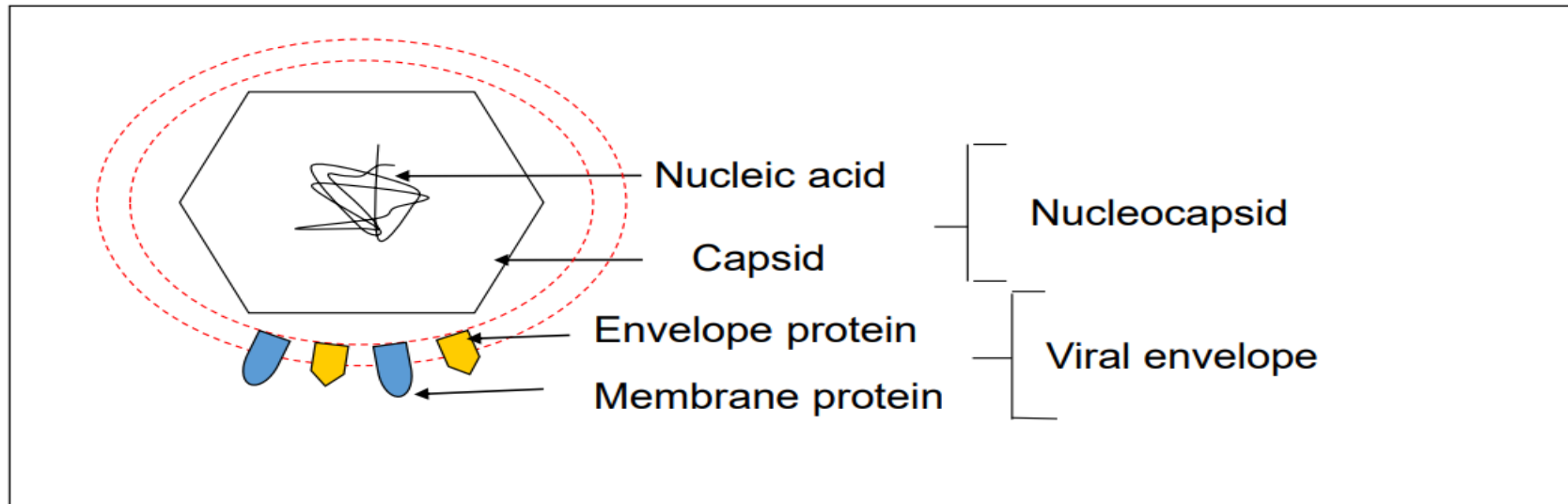
- Nitrogenous bases (Adenine, Cytosine, Guanine, & Uracil)

Type of sugar :
Ribose

- Location :in Nucleus & cytoplasm



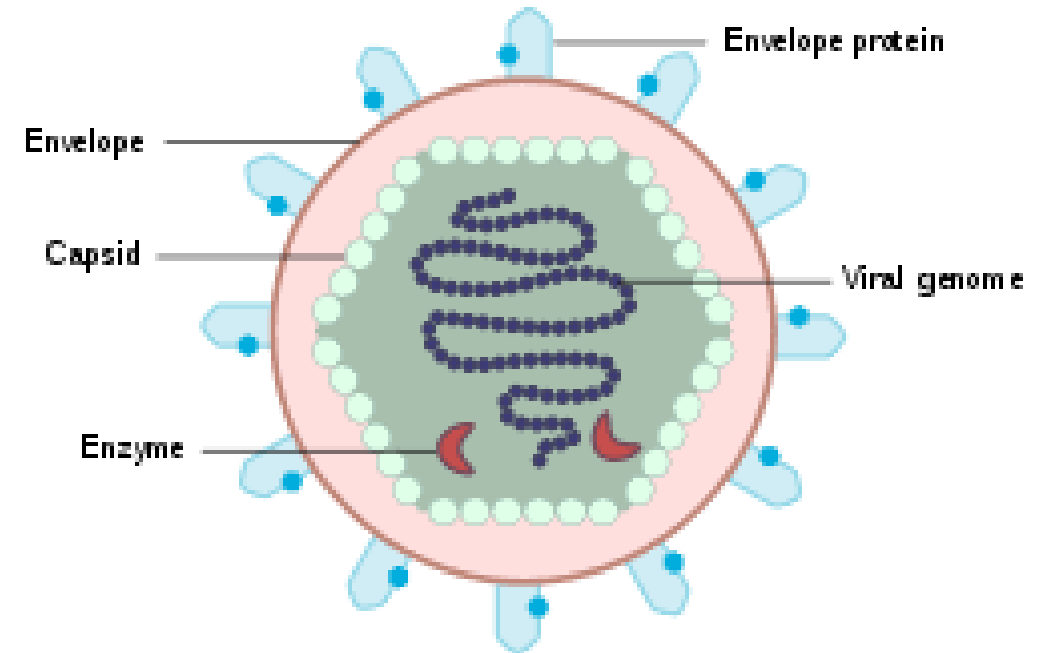
Viral Structure - Overview



The nucleic acid plus the capsid shell of a virus particle is often called nucleocapsid

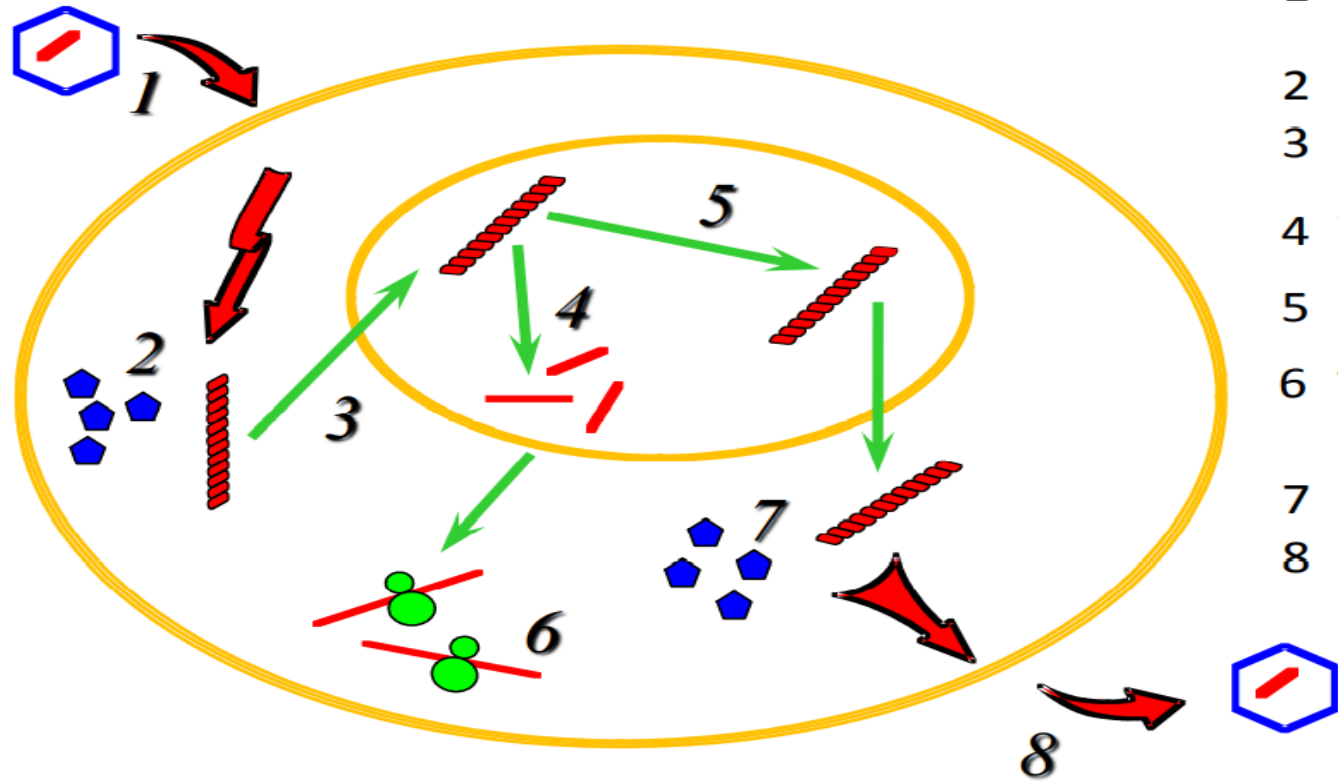
Structure of Viruses:

- Size Between 20-300 nm diameter.
- Basic shape Rod-like ,“Spherical”
- Genomic material : DNA or RNA never both ,Single- or double-stranded



Viral replication:

- A virus cannot replicate on its own
- It must attach to and enter a host cell
- It then uses the host cell's energy to synthesize protein, DNA, and RNA
- Viruses are difficult to kill because they live inside the cells
- Any drug that kills a virus may also kill cells



- 1 Virus attachment
- 2 Penetration
- 3 Uncoating
- 4 Transcription
- 5 Genome replication
- 6 Translation of virus mRNAs
- 7 Virion assembly
- 8 Release of new virus particles

Classification of major virus groups

DNA VIRUSES

1. Herpesvirus
2. Poxvirus
3. Adenovirus
4. Parvovirus
5. Papovavirus

RNA VIRUS

1. Orthomyxovirus
2. Paramyxovirus
3. Rhabdovirus
4. Tagovirus
5. Retrovirus
6. Reovirus
7. Picornavirus
8. Coronavirus

Overview of Viral infections

Encephalitis/ meningitis

- JC virus
- Measles
- LCM virus
- Arbovirus
- Rabies

Common cold

- Rhinoviruses
- Parainfluenza virus
- Respiratory syncytial virus

Eye infections

- Herpes simplex virus
- Adenovirus
- Cytomegalovirus

Pharyngitis

- Adenovirus
- Epstein-Barr virus
- Cytomegalovirus

Gingivostomatitis

- Herpes simplex type 1

Parotitis

- Mumps virus

Pneumonia

- Influenza virus, Types A and B
- Parainfluenza virus
- Respiratory syncytial virus
- Adenovirus
- SARS coronavirus

Cardiovascular

- Coxsackie B virus

Hepatitis

- Hepatitis virus types A, B, C, D, E

Myelitis

- Poliovirus
- HTLV-I

Skin infections

- Varicella zoster virus
- Human herpesvirus 6
- Smallpox
- Molluscum contagiosum
- Human papillomavirus
- Parvovirus B19
- Rubella
- Measles
- Coxsackie A virus

Gastroenteritis

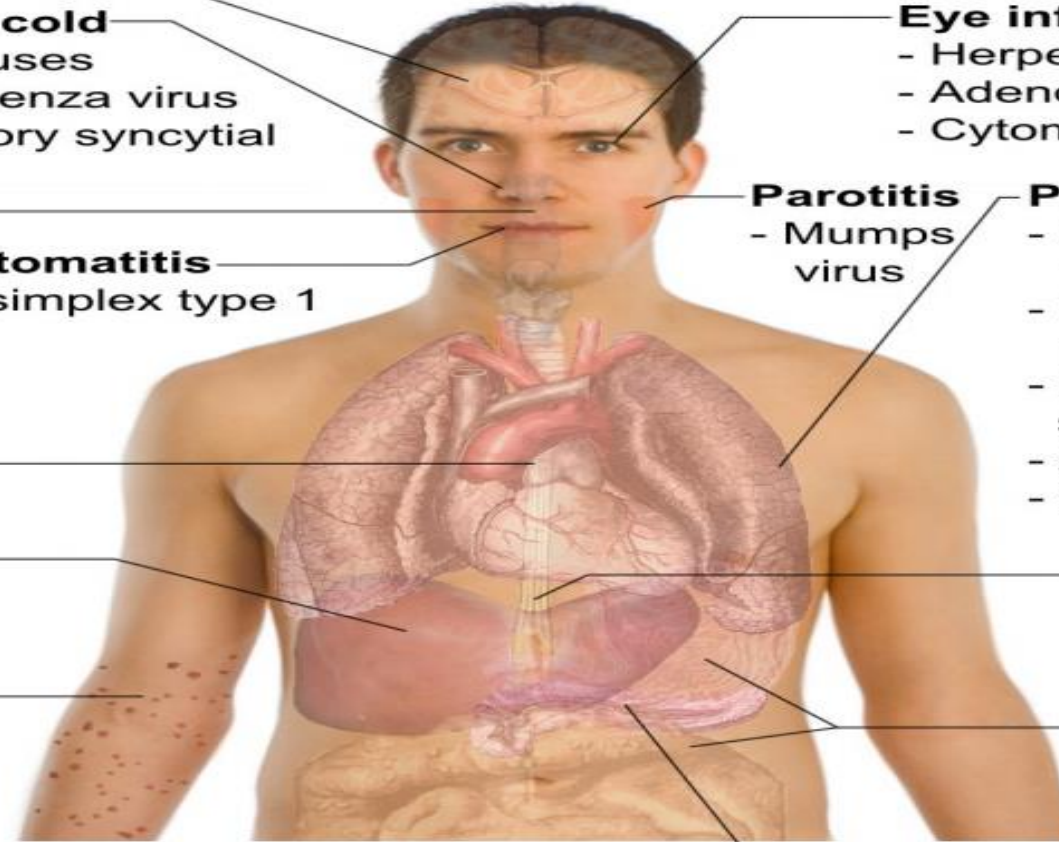
- Adenovirus
- Rotavirus
- Norovirus
- Astrovirus
- Coronavirus

Sexually transmitted diseases

- Herpes simplex type 2
- Human papillomavirus
- HIV

Pancreatitis

- Coxsackie B virus



VIRUS	DISEASE
Adenovirus	Respiratory infections
Epstein barr virus	Infectious mononucleosis Nasopharyngeal carcinoma Burkitt's lymphoma
Herpes simplex Type 1	Cold sores
Herpes simplex Type 2	Genital warts
HIV	AIDS
HPV	Warts
Influenza virus	Influenza

VIRUS	DISEASE
Ebola virus	Haemorrhagic fever
Paramyxo virus	Mumps
Polio virus	Poliomyelitis
Rabies Virus	Rabies
Rubella virus	German measles
Small pox	Small pox
Vericella Zoster	Chicken pox, shingles

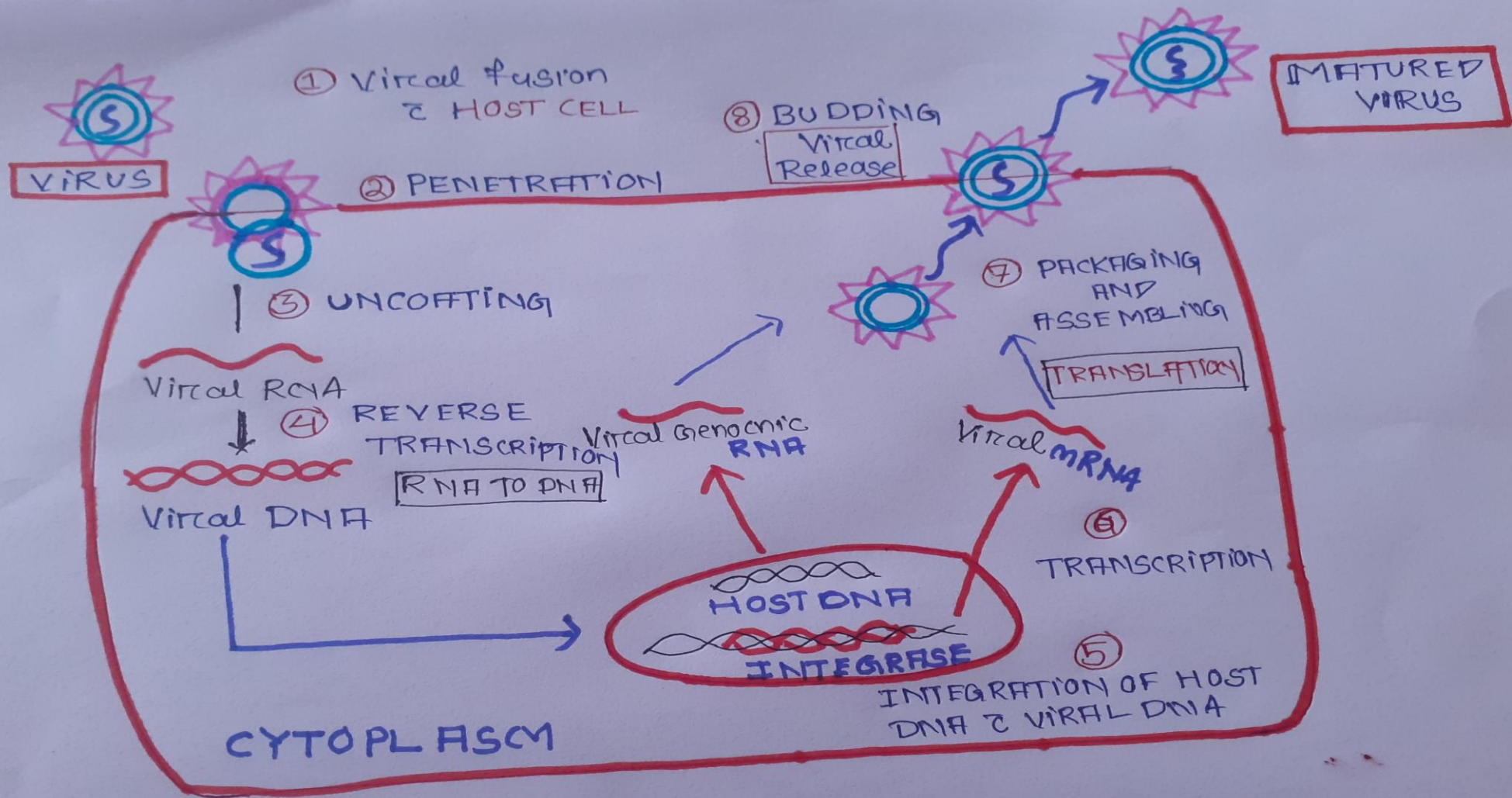
- Viruses have no cell wall and made up of nucleic acid components
- Viruses containing envelope – antigenic in nature
- Viruses are obligate intracellular parasite
- They do not have a metabolic machinery of their own – uses host enzymes
- Certain viruses multiply in the cytoplasm but others do in the nucleus
- Most multiplication take place before diagnosis is made

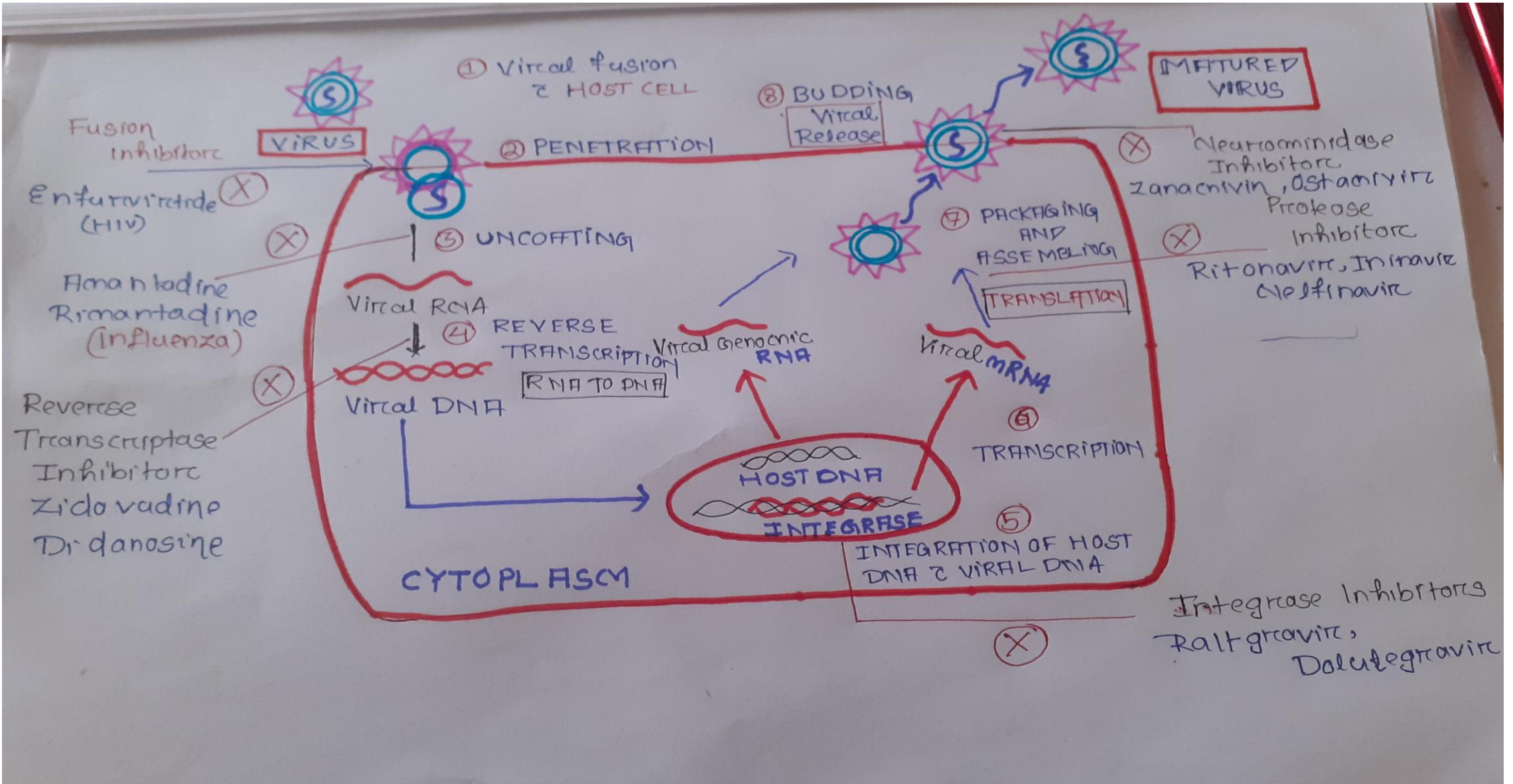
ANTIVIRAL DRUGS :

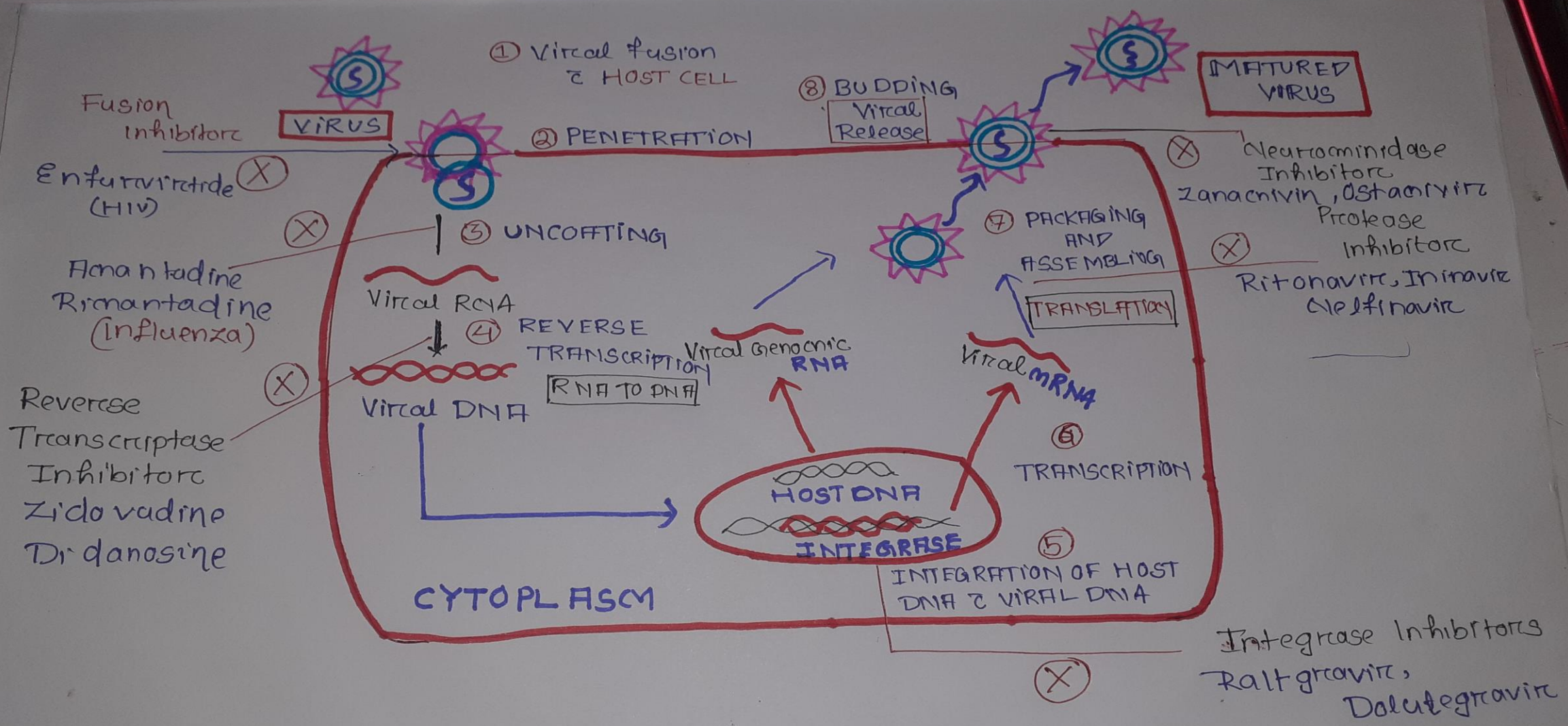
- **Many antiviral drugs are Purine or Pyrimidine analogs.**
- **Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active.**
- **Anti-viral agents inhibits active replication so the viral growth resumes after drug removal.**

• characteristics of antiviral drugs :

- Able to enter the cells infected with virus
- Interfere with viral nucleic acid synthesis and/or regulation
- Some drugs interfere with ability of virus to bind to cells
- Some drugs stimulate the body's immune system
- Best responses to antiviral drugs are in patients with competent immune systems
- A healthy immune system works synergistically with the drug to eliminate or suppress viral activity







Different Methods of Classification = Drug Acting on Viral Replication Steps:

Viral Replication Steps	Effective Drugs
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	Acyclovir, Cidofovir, Famciclovir, Ganciclovir, Foscarnet, Idoxuridin
Replication	NRTIs, NNTTIs, PIs, Ribavirin, Sorivudine
Budding and Release	Zanamivir, Oseltamivir

Different Methods of Classification = According to Clinical Conditions

Clinical Conditions	Drugs used to Treat Clinical Conditions
Herpes Viral Infection	Idoxuridine, Acyclovir, Ganciclovir, Valacyclovir, Famciclovir, Penciclovir, Docosanol, Trifluridine (Purine and Purine Analog)
Cytomegalovirus Infections	Ganciclovir, Valganciclovir, Foscarnet, Cidofovir, Fomivirsen
Anti-Influenza Virus	Amantadine, Rimantadine, Oseltamivir, Zanamivir
Anti-Retroviral Drugs	Zidovudine, Stavudine, lamivudine, Didanosine, Zalcitabine, Emtricitabine, Tenofovir, Delavirdine, Efavirenz, Etravirine, Nevirapine, Amprenavir, Saquinavir, Ritonavir
Drugs for Hepatitis B and Hepatitis C	Interferons, Adefovir, lamivudine, Entecavir, Entecavir, Ribavirin, Sofosbuvir, Ledipasavir

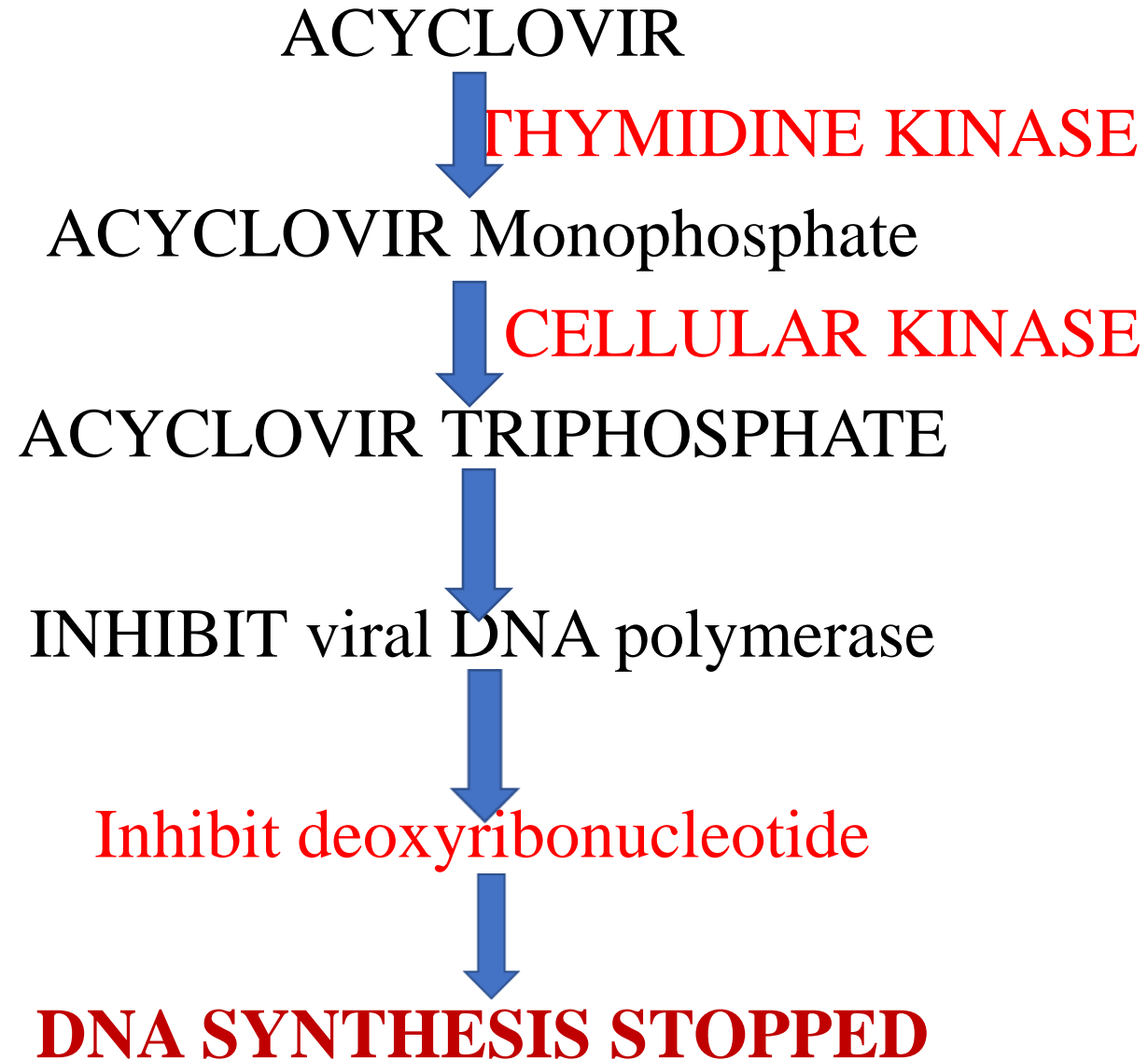
Different Methods of Classification = For Retroviral Infections :

Category	Related Examples
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 (PIs)	Ritonavr, Atazanavir, Indinavir, Nelfinavir, Saquinavir, Fosamprenavir, Lopinavir, Darunavir
Entry Inhibitors	Enfuvirtide
CCR-5 Receptor Inhibitors	Maraviroc
Integrase Inhibitors	Raltegravir, Dolutegravir

ANTIHERPs: ACYLOVIR

- ACTIVE against herpes group of DNA virus(*herpes simplex virus, varicella zoster virus , Epster barr virus*
- **Deoxyguanosine** analogue requires virus specific enzymes for conversion to the active metabolites that *inhibit DNA synthesis and viral replication*

MECHANISM OF ACTION :



INHIBIT viral DNA polymerase competitively



Inhibit deoxyribonucleotide



DNA SYNTHESIS STOPPED



Incorporated with viral DNA & STOP lengthening of DNA strands



Inhibit DNA polymerase irreversibly

- acyclovir preferentially taken up by infected virus cell
- It has low toxicity towards host cell
- Active against herpes group of virus
- Sensitivity : *HSV-I > HSV-II > VZV*
- **HSV & VZV developed resistance**

PHARMACOKINETICS :

- orally 20 % absorbed
- Topically : systemic availability is very less

ADVERSE EFFECTS :

➤ TOPICAL : Stinging and burning sensation

➤ ORAL: Headache, Nausea

➤ IV: rashes , sweating . Emesis , ↓ BP

➤ In dose dependent manner ↓ in GFR

➤ Disorientation, hallucination, convulsion , coma

Till now no teratogenic potential has been reported

USES :

➤ GENETIAL HERPES INFECTION :

- Caused by type-II virus
- Primary disease 5% ointment t applied locally 6 times/day

➤ MUCOCUTANEOUS INFECTION :

- Type –I viral disease remains localized to lips, gum
- Usually do not required specific treatment
- Acyclovir cream is used

➤ **HERPES ZOSTER VIRUS :**

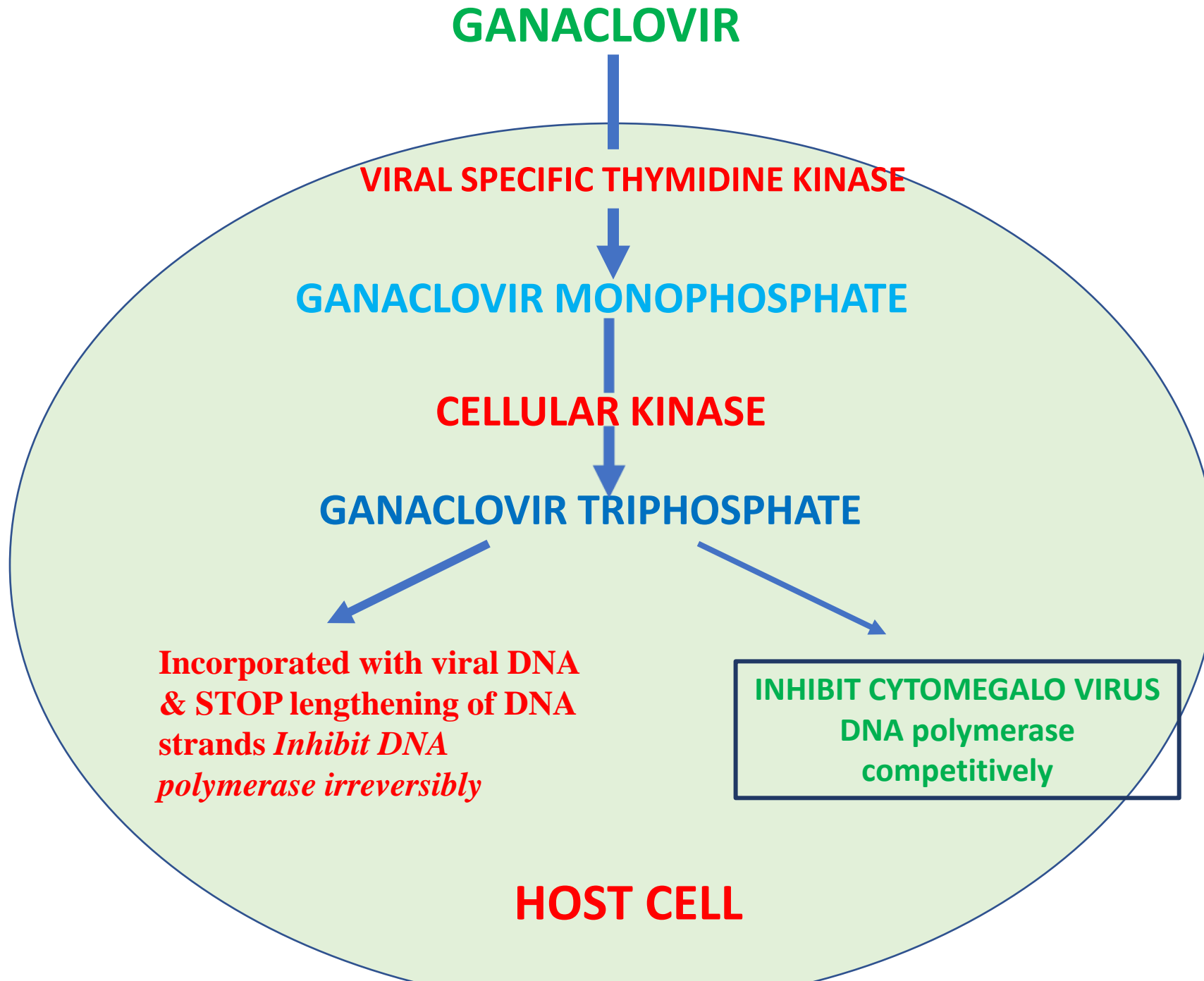
- Less susceptible to acyclovir high dose is required
- It should be used in severe cases and immunodeficient patient
- Dose : 10mg/kg for 7 days

➤ **CHICKEN POX :**

- ADULT : 15mg/kg/day for 7 days
- Decreases severity of disease

GANACLOVIR :Drug for cytomegalo virus

- Analogue of Acyclovir
- Most effective for *cytomegaly virus*
- Activated intracellularly by virus specific enzyme (**Thymidine kinase**)
- It's triphosphate nucleotide preferentially *inhibit viral DNA polymerase*
attains higher conc at infected cell
- Precursor cell in bone marrow are sensitive for Ganaclovir



- Poor oral absorption : **low bioavailability**
- It's prodrug : Valganciclovir
 - Better absorbed orally
- Cytomegaly virus may developed *resistance by mutation of viral phosphokinase and DNA polymerase* (↓ it's effectiveness)

SIDE EFFECTS :HIGH SYSTEMIC TOXICITY

- Bone marrow depression , fever,Rashes ,vomiting, neuropsychiatric disturbance reported

USES: USES IS RESTRICTED

- Used in case of severe infection and prophylaxis which occurs in immunocompromised people
- TREATMENT : IV injection with *10mg/kg/day*
- Prevents blindness in AIDS

ANTIINFLUENZA VIRAL DRUGS:

- **INFLUENZA**: RNA virus with segmented genome and core protein which define it's type **A,B Or C**
- Majority of human infection is caused by **INFLUENZA A**
- CHARACTERIZED BY **HAEMAGGLUTININ-H**
- Produce epidemic & pandemic situations

Neuraminidase-N surface glycoprotein

H5N1-BIRD FLU (1997)
H1N1 SUBTYPE – SWINE FLU
2009

AMANTIDINE : Introduce in 1960s

- Tricyclic amines unrelated to nucleic acid
- Inhibit influenza A virus but not *H5N1, H1N1*
- Act by inhibiting *M2 protein and prevent uncoating of viral genome infected cell*
- Resistance may developed – *on mutation of M2 protein*
- Use is now limited due to *availability of newer & effective drug*
- Use for parkinsonism

OSELTOMIVIR:TAMIFLU

- MOST COMMONLY USED DRUG NOW
- *Sialic acid analogue*
- Spectrum of activity is **broad**
- Cover influenza A with Amantadine resistance and sensitivity
- Includes *H5N1 7 H1N1 & Influenza B*
- OSELTOMIVIR : An ester prodrug that rapidly and fully hydrolysed during absorption in intestine
- By liver esterase it is converted into it's active form

OSELTOMIVIR CARBOXYLATE

- Bioavailability is 80%

MECHANISM OF ACTION :

- Acts by inhibiting Influenza A viral enzyme *NEUROMINIDASE*
- Neuraminidase helps *in release of virus from host cell*
- On inhibition of this *prevents from release of virus from infected cell*
- Resistance may developed by mutation of this enzyme
- Drug regimen should be *started within few hours of discovery of infection*
- It decreases the severity , duration and complication
- May *not be effective in infant* because they may *unable to generate active metabolite*
- **SIDE EFFECTS :** Nausea, abdominal cramps, weakness, headache, sadness, diarrhoea, cough insomnia

ANTIHEPATITIS DRUGS :

HEPATITIS B VIRUS :

- DNA Virus
- Can integrate into host chromosomal DNA to cause permanent infection

HEPATITIS C:



- RNA VIRUS
- DOES'NT integrate into chromosomal DNA
- Does not establish non-curable infection
- But cause hepatitis

RIBAVIRIN & INTERFERON –ALPFA NONSELETIVELY EFFECTIVE AGAINST HEPATITIS B & C

DRUG FOR HEPATITIS C

- Can not be *eradicated completely* from the body
- Treatment : suppression of virus and it's inflammation response
- Sudden stoppage of ANTIHBV can result in **EXACERBATION**
- SHOULD BE USED *UNLESS ANY DEVELOPMENT OF TOXOCITY OR LOSS OF EFFICACY*
- It improved liver function
- Reduction of risk of development of liver cirrhosis and hepatic carcinoma occur.

ADEFOVIR: ADEFOVIR DIPIVOXIL

- Monophosphate analogue of AMP
 - Active against HBV, DNA Or RNA Virus
 - Esterase in the intestine and liver release active drug
- On entering the cell  phosphorylates (diphosphate)
- It has high affinity for HBV DNA polymerase as compared to host cell DNA polymerase
 - It also incorporated into viral DNA results **TERMINATION OF DNA CHAIN** 
 - Used for chronic HEPATITIS B (ALSO FOR LAMIVUDIN RESISTANCE)

SIDE EFFECTS :

- SORE THROATS
- HEADACHE
- WEAKNESS
- FLU SYNDROME
- ABDOMINAL PAIN
- AT HIGH DOSE : *Nephrotoxicity in pt with renal disorder*

well tolerated dose is 10mg/day



DRUG FOR HEPATITIS C: To attain sustained viral response

RIBAVIRIN: Prodrug

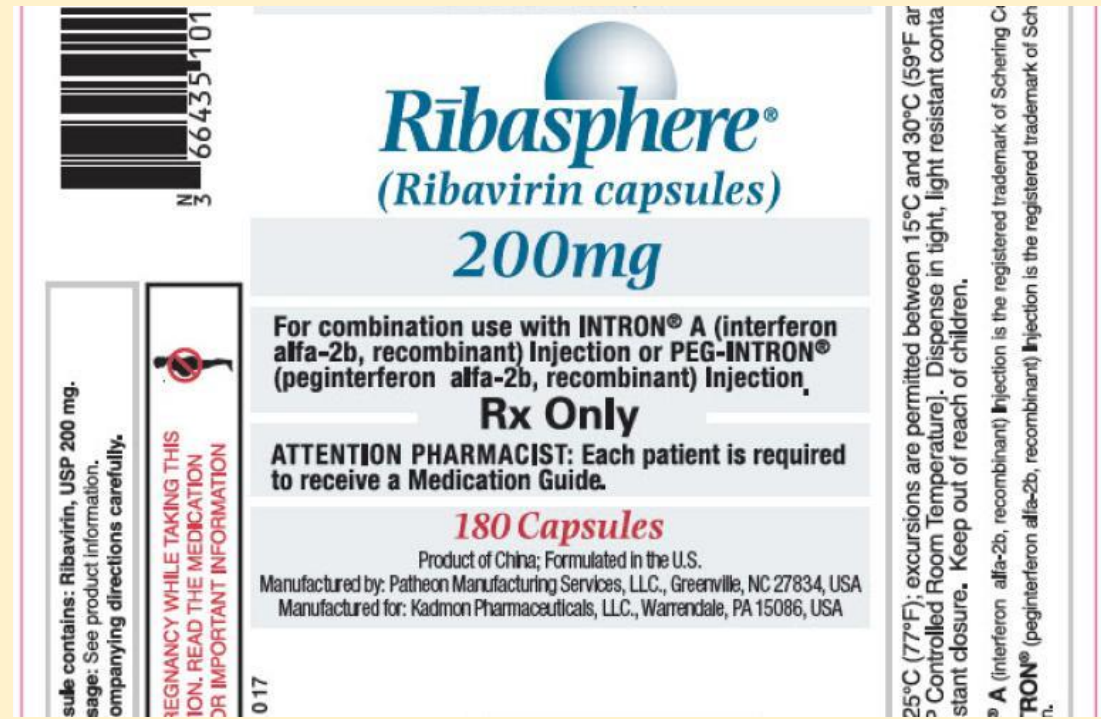
- Purine nucleotide analogue
- Nucleoside inhibitor with broad antiviral activity including HCV (A & B also)
- mono and triphosphate derivative generated intracellularly by host kinase caused inhibition of *GTP Synthesis and viral RNA synthesis*
- Viral resistance is rare, bioavailability is 50%
- Accumulate in body and remains for months even after discontinuation

Use for hepatitis C:

- Shouldn't be used alone
- Combined with infected PEG Interferon for 6 to 12 months
- Active against all genotype of HCV
- ACHIEVE SVR 50-80 %

SIDE EFFECTS:

- Dose dependent hemolytic anemia
- Bone marrow depression
- Headache
- GIT discomfort
- ***SHOW TERATOGENIC EFFECTS***



INTERFERON:

- IT is low m.w glycoprotein cytokines produced by host cell in response to viral infection
- Have nonspecific antiviral and other complex effect on immunity and cell proliferation
- Interferon binds to specific cell surface receptor and affect viral Replication of multiple steps:

- ➔ Penetration
- ➔ Viral mRNA synthesis
- ➔ Assembling of viral particle
- ➔ Release

Widespread of effect is direct or indirect suppression of viral protein synthesis

Inhibition of translation

Interferon are JAK-STAT Tyrosine protein kinase receptor

On activation



Phosphorylates cellular protein

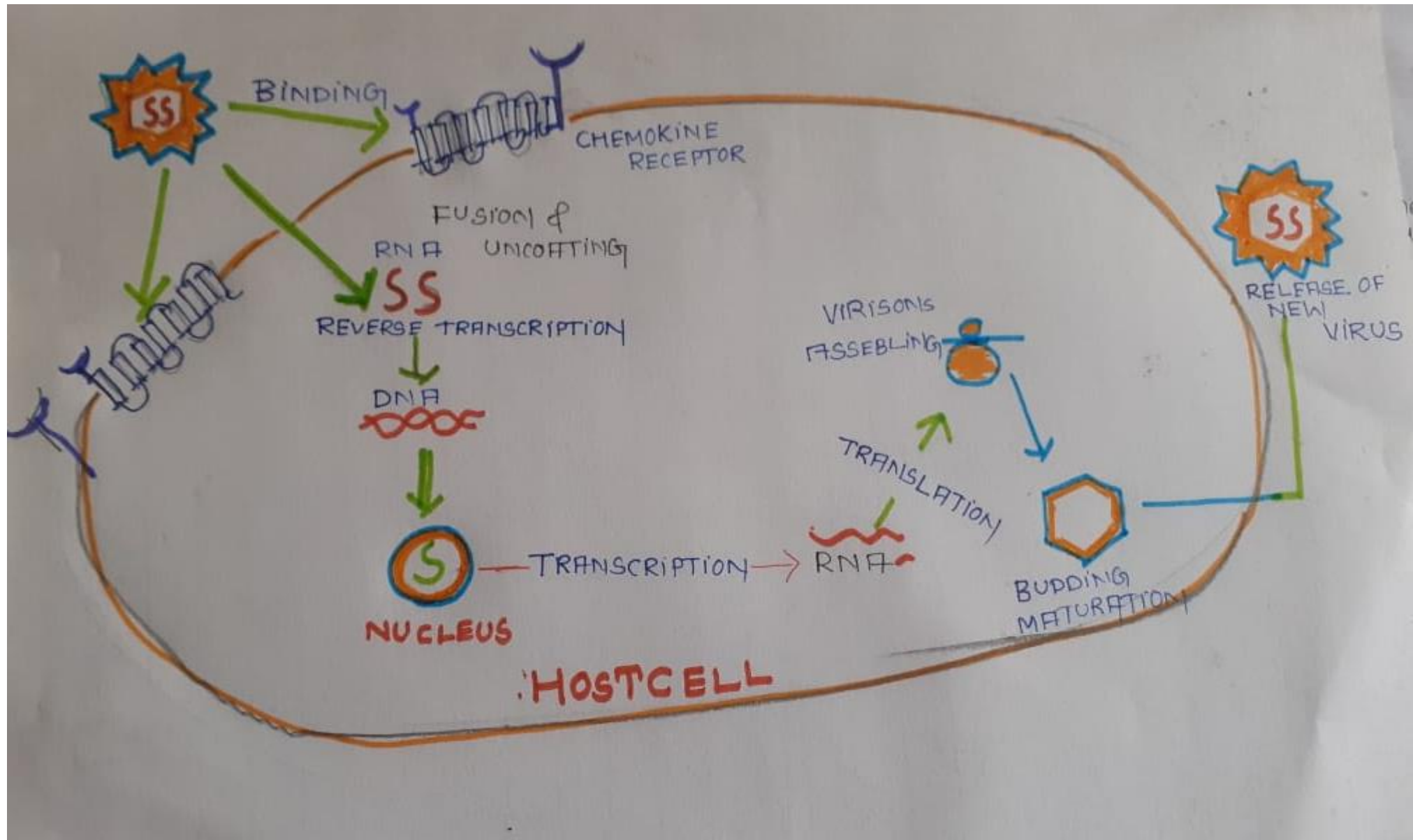
Phosphorylated protein ---migrate to nucleus & starts transcription

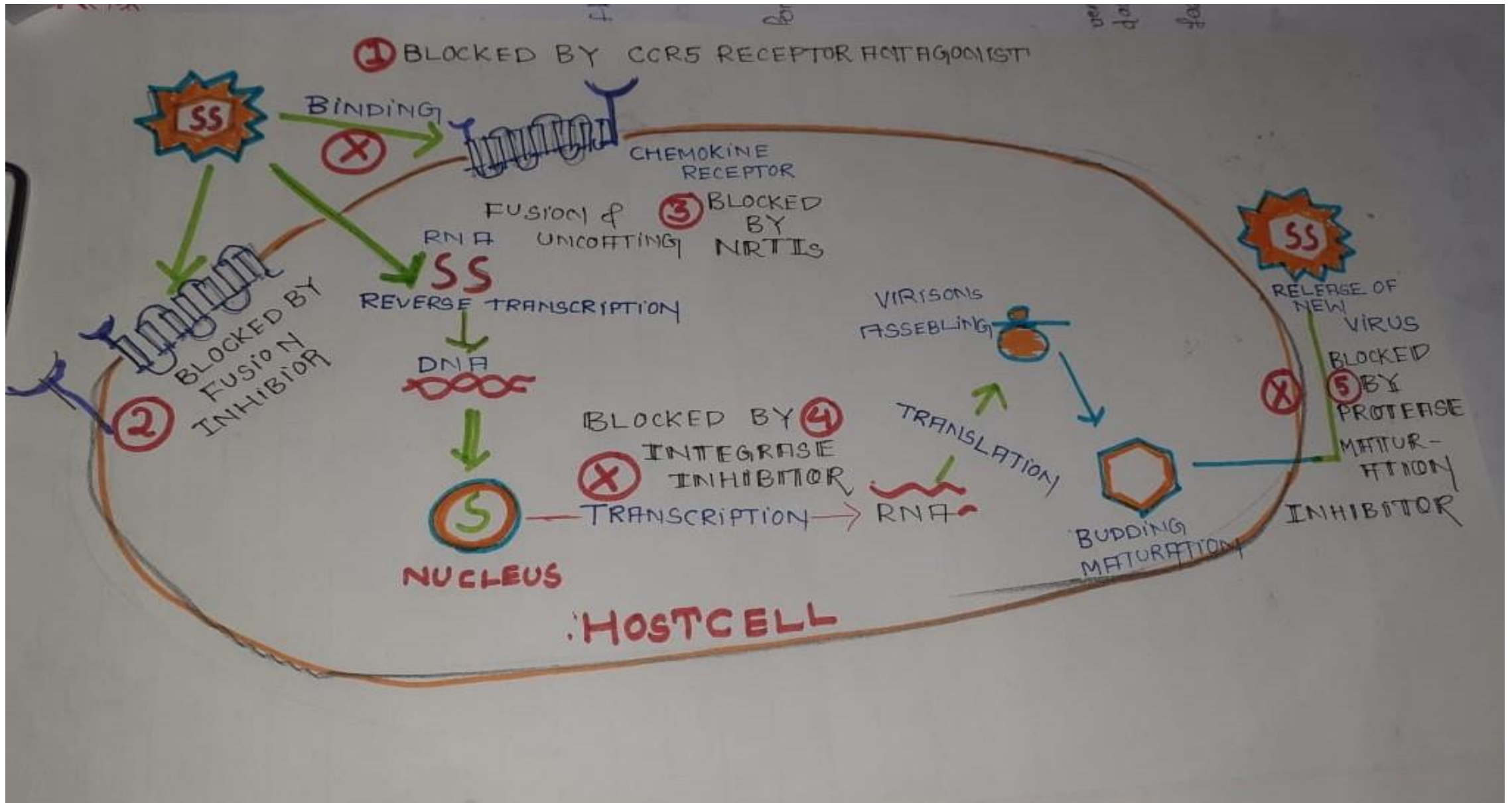
And this interferon induced protein exert antiviral effect

✓ Interferon may inhibit many DNA & RNA virus

- IFN alfa 2A & IFN alfa 2B Produced by RDNA Technology
- Given by SC or IM route







1 BLOCKED BY CCR5 RECEPTOR ANTAGONIST



BINDING



CHEMOKINE RECEPTOR

3 BLOCKED BY NRTIS

FUSION & RNA UNCOATING

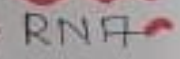
SS REVERSE TRANSCRIPTION



NUCLEUS

4 BLOCKED BY INTEGRASE INHIBITOR

TRANSCRIPTION



TRANSLATION



VIRIONS ASSEMBLING

BUDDING MATURATION

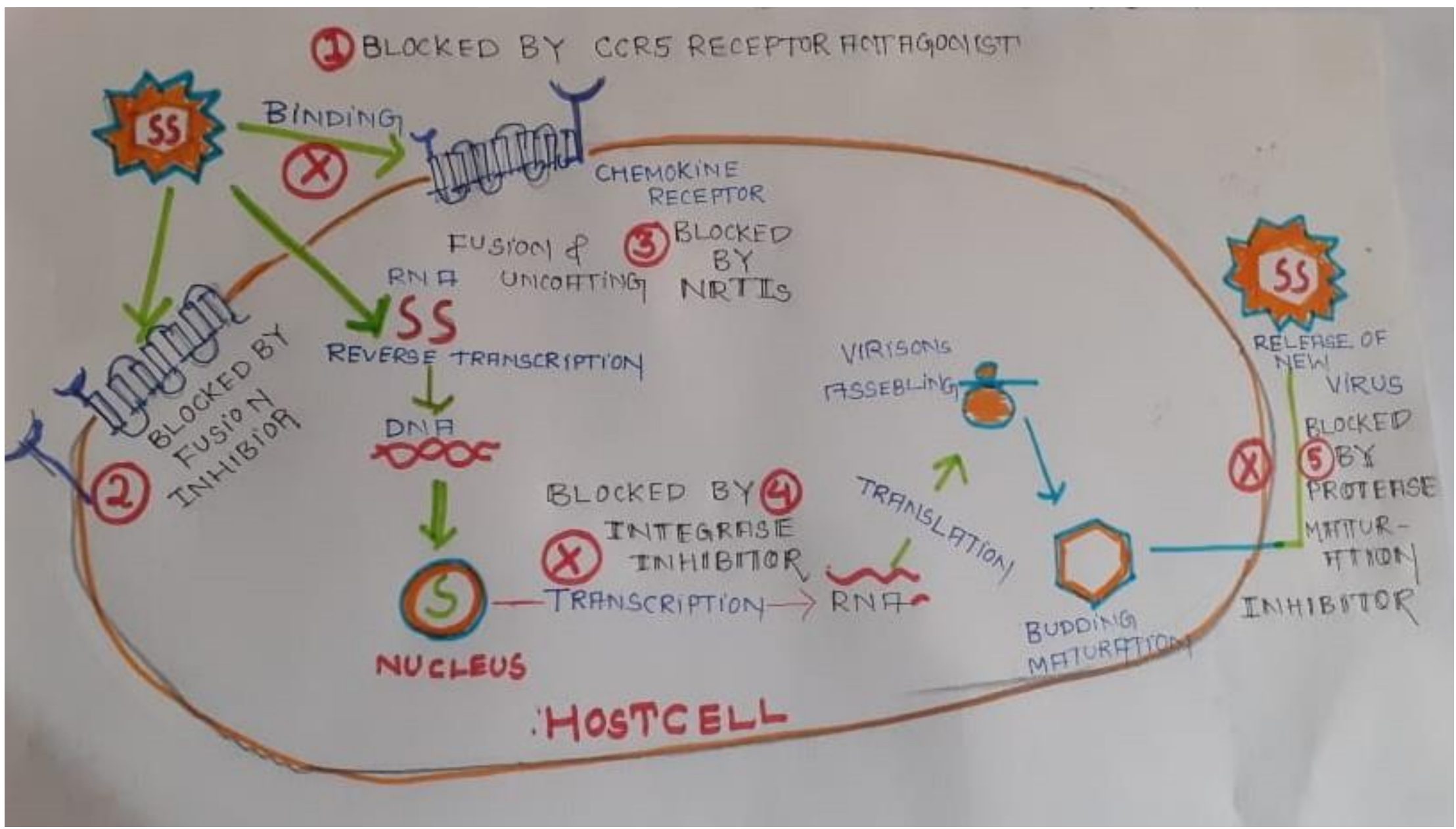


RELEASE OF NEW VIRUS

5 BLOCKED BY PROTEASE MATURATION INHIBITOR


2 BLOCKED BY FUSION INHIBITOR

HOST CELL



ZIDOVUDIN : Thymidine analogue

- First prototype of NRTIs
- After phosphorylation (in host cell)--- Zidovudine triphosphate
- Zidovudine triphosphate selectively decreases viral reverse transcriptase in preference to Cellular DNA polymerase

- 

SINGLE STRANDED VIRAL RNA **ZIDOVUDINE** → DOUBLE STRANDED PROVIRAL DNA
REVERSE TRANSCRIPTASE ENZYME

- Proviral DNA translocate to nucleus & is integrated with chromosomal DNA of host cell
- Under direction of m RNA viral regulatory and structural protein are formed in the form of polyprotein:
- Finally viral particles are assembled & matured to be released
- Zidovudine prevents infection of new cell from HIV but no effect on proviral DNA that has already integrated into host chromosomal DNA
- Active against retroviral disease only
- Zidovudine itself incorporated into proviral DNA & Terminate chain elongation
- Resistance may be developed on mutation, affect reverse transcriptase activity

- PHARMACOKINETICS :
- Rapidly absorbed through oral route
- Bioavailability 60 %
- It may cross blood placenta barrier

ADVERSE DRUG REACTION:

- Bone marrow depression, Anemia
- Neutropenia, Nausea, anorexia, headache Abdominal pain, insomnia
- Infrequent : myopathy, abdominal pain, nail pigmentation, hepatomegaly

DRUG INTERACTION:

- Paracetamol increases toxicity
- STARVUDIN & ZIDOVUDIN : Exhibit mutual antagonism by competing for the same binding pathway
- Nephrotoxic drugs increases toxicity
- Azole antifungal drugs decreases metabolism increases toxicity

USES:

- In HIV infected patient
- No longer included in 1st line drug by WHO REGIMEN (2016)

RETROVIRAL PROTEASE INHIBITOR:

PROTEASE:

- HIV specific enzyme
- Aids in production of structural protein and enzyme including reverse transcriptase, integrase
- It is formed from the virus polyprotein in infected cell
- It also acts in late step in HIV Replication (maturation)

PROTEASE INHIBITORS:

ATAZANAVIR, IMDINAVIR, RITONAVIR

- Bind to active site of protease molecule , interfere with it's clearing
- More effective than zidovudine
- Don't need intracellular activation by phosphorylation
- Effective for both new & chronically infected cell
- *Combination of NRTIs with protease inhibitors is more effective*

ADVERSE DRUG REACTION:

GIT Disturbances , headache , dizziness, rashes, tingling of nail & facial parts, numbness, rashes

Drug	description
ATAZANAVIR	<p>Administered with light meal , increase abs Antacid decrease abs BA & EFFICACY INCREASE BY COMBINING WITH RITONAVIR ADR: Nausea, diarrhea, Jaundice, Abdominal pain</p>
INDINAVIR	<p>Has to be taken at empty stomach Excess fluid must be consumed to avoid nephrolithiasis</p>
RITONAVIR	<p>Potent protease inhibitor Used to boost other protease inhibitor Nausea , diarrhea , fatigue are common</p>
DARANAVIR	<p>Newest protease inhibitors useful in several resistance B.A. can be improved by co-administering Ritonavir (retards 1st pass metabolism & systemic clearance decreases Rifampin makes it's less effective Approved for use only in combination with Ritonavir or other booster</p>

INTEGRASE INHIBITORS:

- HIV integrase enzyme enter host cell along with genomic DNA
- After *HIV proviral DNA is transcribed in cytoplasm of host cell, this enzyme translocate to nucleus along with proviral DNA*
- Host chromosomal DNA ,integrase the proviral DNA with it resealed it
- Thus proviral DNA becomes a part of chromosomal DNA (Cell get permanently infected)
- Integrase inhibitors : *inhibit this process of virus*

RALTEGRAVIR :

- 1ST Integrase inhibitor available to Treat HIV
- Prevent integration of proviral DNA into host chromosomal DNA
- Interrupt viral cycle
- Useful for **both HIV-I & HIV-II**
- No cross resistance with other class of antiviral drugs
- Clear HIV RNA from circulation
- Antacid containing *Ca+2, Mg+2 or iron substance shouldn't taken together*
- **Side effects :** nausea , headache, diarrhoea , weakness, myopathy

ENTRY or FUSION INHIBITOR : ENFUVIRTIDE:

- HIV derived synthetic peptide acts by binding to HIV-I envelope transmembrane glycoprotein
- Involved in fusion of viral and cellular membrane
- *Fusion of two membrane is prevented & entry of virus into the cell is blocked*
- Not active against HIV-II
- No cross resistance with other class of **ANTIVIRAL DRUG**
- Administered S.c twice daily
- Used as add on to other resistance