ANTI-VIRAL DRUGS

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INTRODUCTION

- Viruses shore many of the metabolic processes of the host cells, it is difficult to find drugs that are selective for the pathogens.
- Most currently available antiviral agents are only effective while the virus is replicating (make an exact copy of; reproduce).
- Viruses are obligate intracellular parasites.
- They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes.
- Viral reproduction uses much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the host.
- Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated.

- At this late, symptomatic stage of the viral infection, administration of drugs that block viral replication has limited effectiveness. However, some antiviral agents are useful as prophylactic (intended to prevent) agents.
- Viruses are obligate intracellular parasites that use many of the host cell's biochemical mechanisms and products to sustain their viability.
- A mature virus (virion) can exist outside a host cell and still retain its infective properties.
- However, *to reproduce, the virus must enter the host cell, take over the host cell's mechanisms for nucleic acid and protein synthesis, and direct the host cell to make new viral particles.*

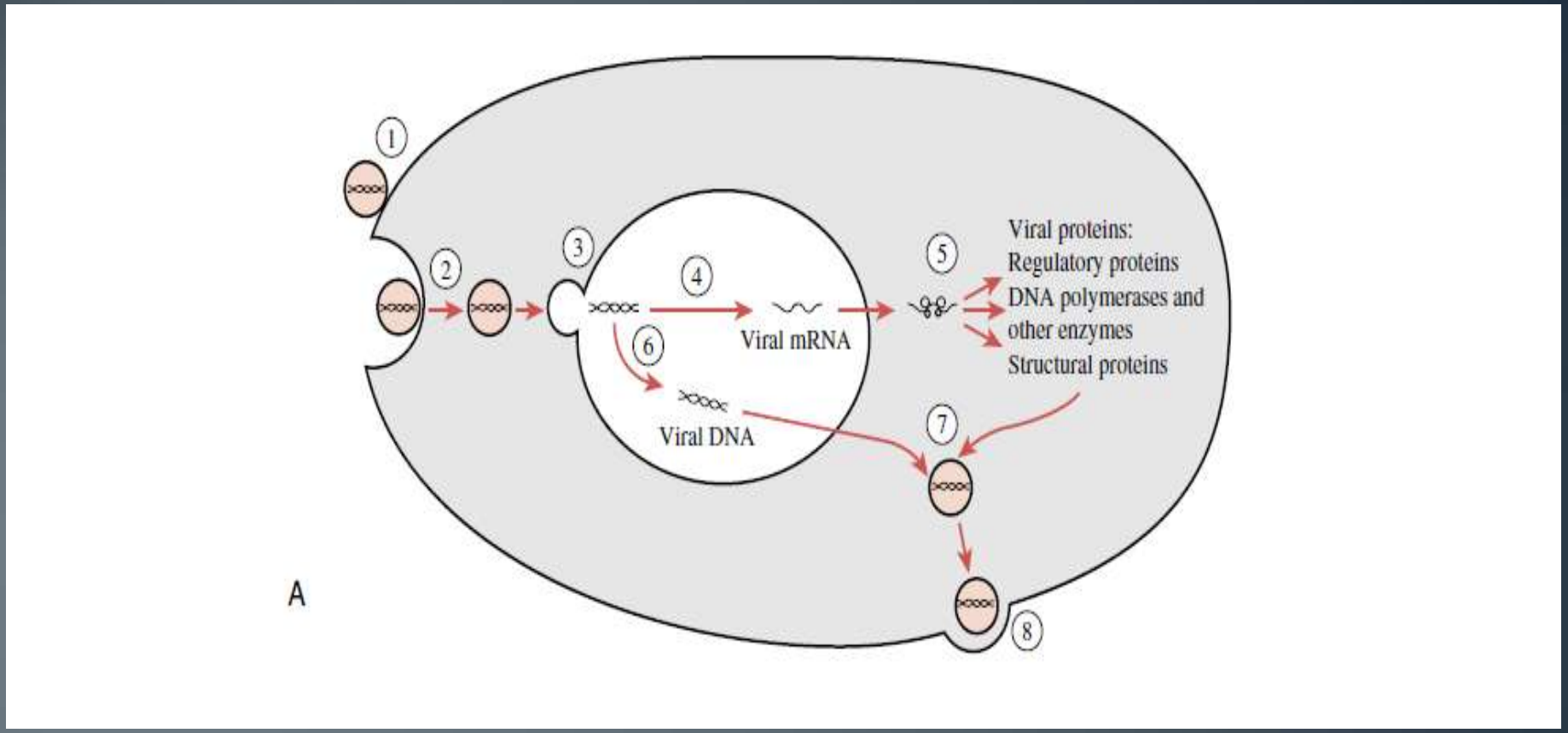
CLASSIFICATION OF VIRUSES

- Viruses are composed of one or more strands of a nucleic acid (core) enclosed by a protein coat (capsid).
- Many viruses possess an outer envelope of protein or lipoprotein.
- Viral cores can contain either DNA or RNA; thus, viruses may be classified as DNA viruses or RNA viruses.
- Further classification is usually based on:
  - Morphology,
  - Cellular site of viral multiplication, or
  - Other characteristics
    - Size of virions
    - Type of host
    - .

- At Rio de Janeiro in 1950 the Virus Subcommittee of the International Nomenclature Committee suggested eight criteria to be used in classifying viruses :
  1. Morphology and methods of reproduction.
  2. Chemical composition and physical properties.
  3. Immunological properties.
  4. Susceptibility to physical and chemical agents.
  5. Natural methods of transmission.
  6. Host, tissue and cell tropisms.
  7. Pathology including inclusion-body formation.
  8. Symptomatology .

DNA VIRUS	RNA VIRUS
Adenoviruses (Colds, Conjunctivitis)	Arborviruses (Tick-borne Encephalitis, Yellow Fever)
Hepadnaviruses (Hepatitis B)	Arenaviruses (Lassa Fever, Meningitis)
Herpesviruses (Cytomegalovirus, Chickenpox, Shingles)	Orthomyxoviruses (Influenza)
Papillomaviruses (Warts)	Picornaviruses (Polio, Meningitis, Colds)
Poxviruses (Smallpox)	Rhabdoviruses (Rabies)
-	Rubella Virus (German Measles or Rubella)
-	Retroviruses (AIDS)

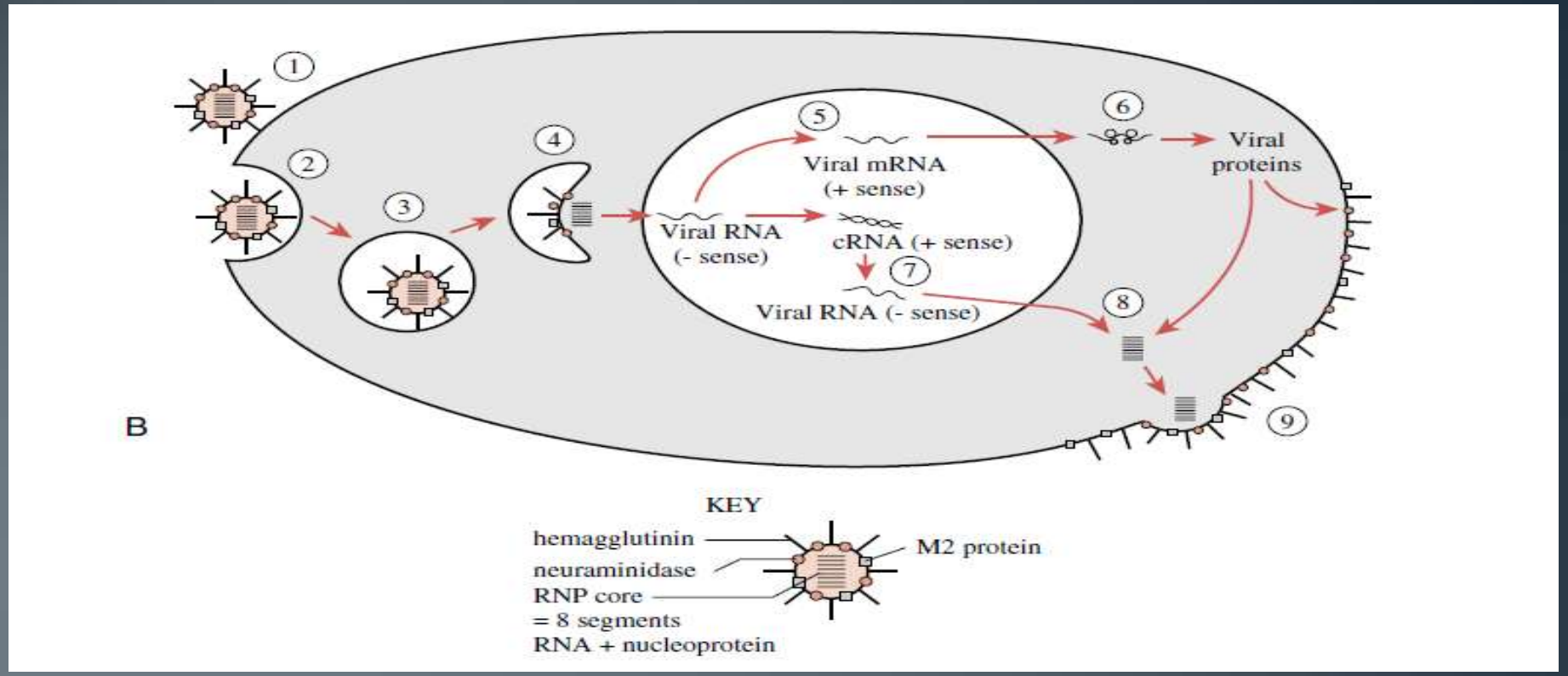
- Infection begins when specific receptor sites on the virus recognize corresponding surface proteins on the host cell.
- The virus penetrates the host membrane by a mechanism resembling endocytosis and is encapsulated by the host cell’s cytoplasm, forming a vacuole.
- Next, the protein coat dissociates and releases the viral genome, usually into the host cell’s nucleus. Following the release of its genome, the virus synthesizes nucleic acids and proteins in sequence.
- In DNA viruses, the first genes to be transcribed are the immediate–early genes.
- These genes code for regulatory proteins that in turn initiate the transcription of the early genes responsible for viral genome replication.
- After the viral DNA is replicated, the late genes are transcribed and translated, producing proteins required for the assembly of the new virions.



REPLICATIVE CYCLE OF A HERPESVIRUS, AN EXAMPLE OF A DNA VIRUS.

1. Attachment.
2. Membrane fusion.
3. Release of viral DNA through nuclear pores.
4. Transcription of viral mRNA.
5. Synthesis of viral proteins by host cell's ribosomes.
6. Replication of viral DNA by viral polymerases.
7. Assembly of virus particles. *8.* Budding and release of progeny virus.

- RNA viruses have several major strategies for genome replication and protein expression.
- Certain RNA viruses contain enzymes that synthesize messenger RNA (mRNA) using their RNA as a template; others use their own RNA as mRNA.
- The retroviruses use viral reverse transcriptase enzymes to produce DNA using viral RNA as a template.
- The newly synthesized DNA integrates into the host genome and is transcribed into mRNA and genomic RNA for progeny virions.
- Following their production, the viral components are assembled to form a mature virus particle.
- The viral genome is encapsulated by viral protein; in some cases (e.g. adenovirus, poliovirus), it is not encapsulated.
- In certain viruses, such as the poxviruses, multiple membranes surround the capsid. Release of the virus from the host cell may be rapid and produce cell lysis and death.



REPLICATIVE CYCLE OF AN INFLUENZA VIRUS, AN EXAMPLE OF AN RNA VIRUS.

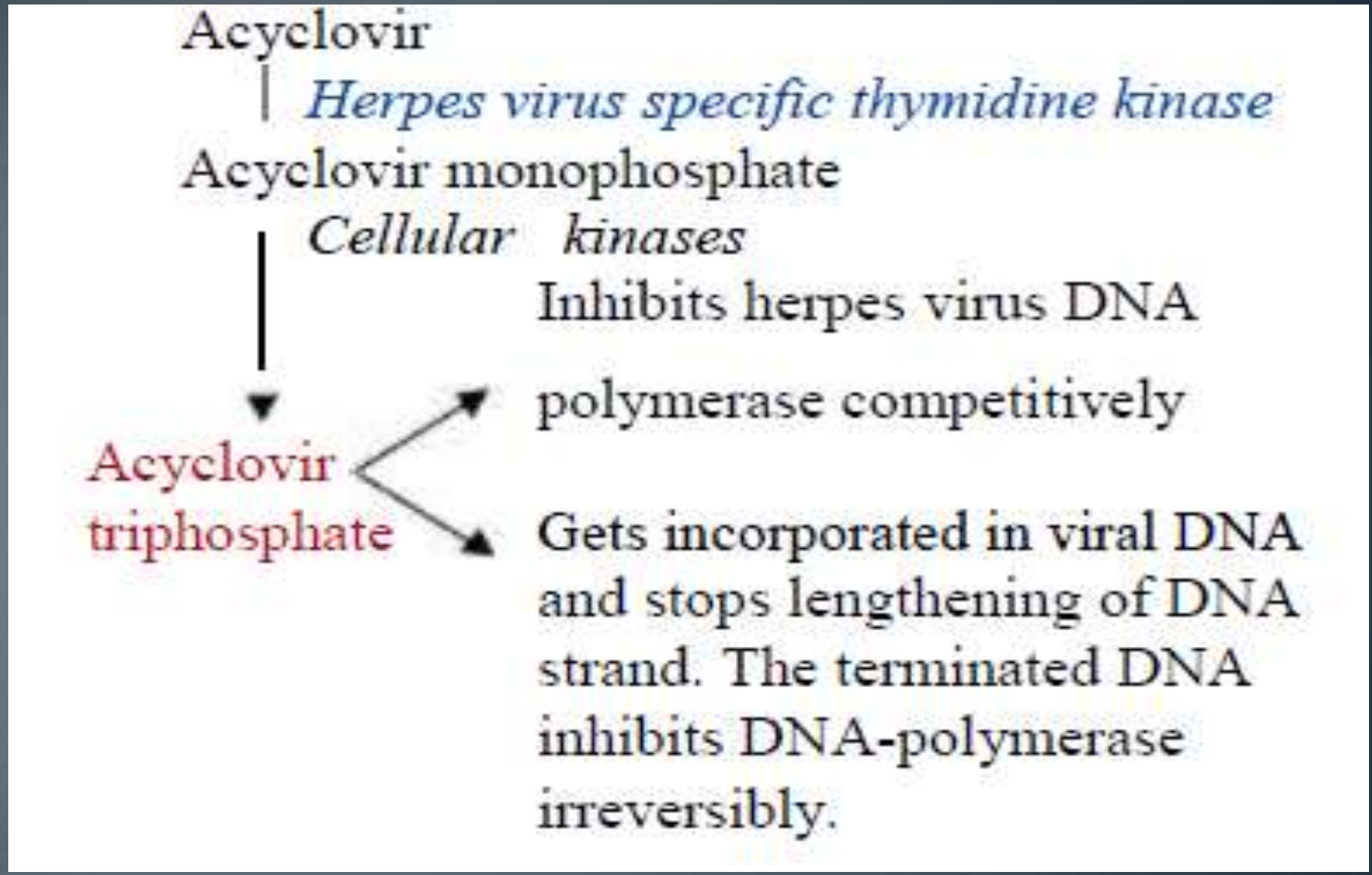
1. Attachment.
2. Endocytosis.
3. Influx of H through M2 protein.
4. Fusion of the viral envelope with the endosomes membrane, dissociation of the RNP **(Ribonucleoprotein)** complex, and entry of viral RNA into the nucleus.
5. Synthesis of viral mRNA by viral RNA polymerase.
6. Translation of viral mRNA by host cell's ribosomes.
7. Replication of viral RNA, using viral RNA polymerase, via cRNA replicative form.
8. Assembly of virus particles.
9. Budding and release of progeny virus.

CLASSIFICATION OF ANTI VIRAL AGENTS

1. **ANTI HERPES VIRUS:** ex. Idoxuridine, Acyclovir, Foscarnet
2. **ANTI - RETRO VIRUS:**
   a) **NRTIs:** ex. Zidovudine, Zalcitabine, Abacavir
   b) **NNRTIs:** ex. Nevirapine, Efavirenz, Delavirdine
   c) **PROTEASE INHIBITORS:** ex. Ritonavir, Indinavir, Lopinavir
   d) **ENTRY (FUSION) INHIBITOR:** ex. Enfuvirtide
   e) **CCR5 RECEPTOR INHIBITOR:** ex. Maraviroc
   f) **INTEGRASE INHIBITOR:** ex. Raltegravir
3. **ANTI – INFLUENZA VIRUS:** ex. Amantidine, Rimantadine
4. **ANTI – HEPATITIS VIRUS / NON – SELECTIVE ANTIVIRAL AGENTS:** ex. Ribavirin, Adefovir, Interferon α

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).
- **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 in DNA so that faulty DNA is formed which breaks down easily. It is effective only against DNA viruses and clinical utility is limited to topical treatment of *Herpes simplex* keratitis.
- **ACYCLOVIR:** This deoxyguanosine analogue antiviral drug requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication.



MECHANISM OF ACTION OF ACYCLOVIR

- Acyclovir is preferentially taken up by the virus infected cells.
- Because of selective generation of the active inhibitor in the virus infected cell and its greater inhibitory effect on viral DNA synthesis, acyclovir has low toxicity for host cells; a several hundred-fold chemotherapeutic index*(the ratio of the maximum tolerated dose of a chemical agent used in chemotherapy to its minimum effective dose)* has been noted.

ANTI-BACTERIAL SPECTRUM:

- Acyclovir is active only against herpes group of viruses; HSV-1(Herpes simplex virus-1) is most sensitive followed by HSV-2(Herpes simplex virus-2) > VZV (Varicella-Zoster virus)=EBV(Epstein-Barr virus), while CMV(Cytomegalovirus) is practically not affected.

RESISTANCE:

- HSV and VZV have been found to develop resistance to acyclovir during therapy; the former primarily due to mutants deficient in thymidine kinase activity and the latter primarily by change in specificity of virus directed enzyme so that its affinity for acyclovir is decreased.

PHARMACOKINETICS:

- Absorption: Orally, Intravenously, Topically
  - When administered orally 20% dose absorbed and Peak Concentration achieved within 1 – 2 hr.
- Distribution: Widely Distributed
  - CSF concentration which are 50% of those in the plasma.
  - After topical application, it penetrates cornea well.
- Excretion: Unchanged in Urine
  - Primarily excreted unchanged in urine, both by glomerular filtration and tubular secretion.
  - $t_{1/2}$ is 2 – 3 hrs.

CLINICAL USES:

- Genital herpes simplex
- Mucocutaneous
- H. simplex encephalitis
- H. simplex keratitis
- Herpes zoster
- Chicken pox

ADVERSE EFFECTS

ORAL	TOPICAL	PARENTRALLY
Headache	Stinging (injury caused by a poisonous substance)	Rashes
Nausea	Burning	Sweating
Malaise		Emesis
CNS effects		Hypotension
		Decrease g.f.r
		Tremors
		Lethargy
		Disorientation
		Hallucinations
		Convulsions
		Coma

ANTI-RETROVIRUS DRUGS

- These are drugs active against human immunodeficiency virus (HIV) which is a retrovirus.
- They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC), but *do not cure the infection*.
- The clinical efficacy of anti-retrovirus drugs is monitored primarily by plasma HIV-RNA assays and CD4 lymphocyte count carried out at regular intervals.
- A number of virus specific targets have been identified and drugs for these developed. Now, drugs which effectively suppress HIV replication and restore CMI for variable periods of time. The two established targets for anti-HIV attack are:
  - **HIV reverse transcriptase:** Which transcripts HIV-RNA into proviral DNA.
  - **HIV protease:** Which cleaves the large virus directed polyprotein into functional viral proteins.

MECHANISM OF HIV

- HIV is a single stranded RNA retrovirus which uniquely carries out reverse transcription of proviral DNA from viral RNA (normally RNA is transcripted from DNA) with the help of a viral RNA-dependent DNA polymerase (reverse transcriptase).
- The primary cell type attacked by HIV is the CD4+ helper T-lymphocyte, but later macrophages and some other cell types may also be infected.
- When population of CD4 cells declines markedly (<200 cells/μL), cell mediated immunity (CMI) is lost and opportunistic infections abound, to which the victim ultimately succumbs, unless treated.
- Because the HIV genome integrates with the host DNA, eradication of the virus from the body of the victim appears impossible at present.

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

- Highly active antiretroviral therapy (HAART) are medications used to treat HIV infection. These medications may also be called antiretroviral drugs (ART), anti-retrovirals(ARVs), or anti-HIV drugs.
- HAART prevents the HIV virus from making copies of itself and limits how much virus is in the body. The level of virus in the blood is called ‘viral load’.
- When the viral load is low, there is less harm to the body’s immune system and fewer complications of HIV infection. Reducing the viral load to "undetectable" levels also reduces the chance of passing HIV to partners.
- There are different kinds of HAART available for treatment. Today HAART is easy to take and the number of pills needed are less than in the past.

DRUGS USED IN HAART:

- There are currently five classes of antiretroviral drug, each of which inhibits a specific stage in the HIV life cycle:
- Entry or fusion inhibitors (which include CCR5 receptor antagonists)
  - Enfuvirtide (Fusion): Maraviroc (CCR5)
- Nucleoside and nucleotide reverse transcriptase inhibitors
  - Abacavir, Lamivudine, Tenofovir, Stavudine, Zidovudine etc.
- Non-nucleoside reverse transcriptase inhibitors
  - Rilpivirine, Delavirdine, Efavirenz, Etravirine, Nevirapine,
- Integrase inhibitors
- Protease inhibitors
  - Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir + ritonavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir

MONOCLONAL ANTIBODY	FIXED-DOSE COMBINATIONS
Atazanavir + cobicistat	Abacavir + dolutegravir + lamivudine,
Darunavir + cobicistat	Abacavir + lamivudine,
Elvitegravir + TDF + FTC + cobicistat	Abacavir + lamivudine + zidovudine,
Elvitegravir + TAF + FTC + cobicistat	Atazanavir + cobicistat,
	Atazanavir + cobicistat,
	Bictegravir + emtricitabine + tenofovir alafenamide,
	Dolutegravir + rilpivirine,
	Durunavir + cobicistat,
	Efavirenz + emtricitabine + tenofovir,
	Elvitegravir + cobicistat + emtricitabine + tenofovir,
	Elvitegravir + cobicistat + emtricitabine + tenofovir,
	Emtricitabine + rilpivirine + tenofovir,
	Emtricitabine + rilpivirine + tenofovir,
	Emtricitabine + tenofovir,
	Lamivudine + zidovudine,

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)

Zidovudine:

- It is a thymidine analogue (azidothymidine, AZT), the prototype NRTI. After phosphorylation in the host cell—zidovudine triphosphate selectively inhibits viral reverse transcriptase in preference to cellular DNA polymerase.
- On the template of single-stranded RNA genome of HIV, a double-stranded DNA copy is produced by viral reverse transcriptase.
- This proviral DNA translocates to the nucleus and is integrated with chromosomal DNA of the host cell (by viral integrase enzyme) which then starts transcribing viral genomic RNA as well as viral mRNA.
- Under the direction of viral mRNA, viral regulatory and structural proteins are produced in the form of a polyprotein.
- Finally, viral particles are assembled and matured after fractionation of the polyprotein by viral protease.
- Zidovudine thus prevents infection of new cells by HIV, but has no effect on proviral DNA that has already integrated into the host chromosome.

ANTI – BACTERIAL SPECTRUM:

- It is effective only against retroviruses. Zidovudine itself gets incorporated into the proviral DNA and terminates chain elongation.
- Resistance to AZT occurs by point mutations which alter reverse transcriptase enzyme. In the past, when AZT was used alone, >50% patients became nonresponsive to AZT within 1–2 years therapy due to growth of resistant mutants.

PHARMACOKINETICS:

- The oral absorption of AZT is rapid, but bioavailability is ~65%.
- It is quick cleared by hepatic glucuronidation ($t_{1/2}$ 1 hr); 15– 20% of the unchanged drug along with the metabolite is 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 EFFECTS:

- Anaemia
- Neutropenia
- Nausea
- Anorexia
- Abdominal pain
- Headache
- Insomnia
- Myalgia
- Myopathy
- Lactic acidosis
- Hepatomegaly
- Convulsions
- Encephalopathy

THERAPEUTIC USES:

- HIV infected patients
- Reduced neurological manifestations

INTERACTIONS:

- PCM increase Zidovudine toxicity by competing for glucuronidation.
- Azoles dvts of anti-fungal drugs also inhibit AZT metabolism.
- Other nephrotoxic and myelosuppressive drugs and probencid enhance toxicity.
- Stavudine and AZT exhibit mutual antagonism by competing for the same activation pathway.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)

NEVIRAPINE (NVP) AND EFAVIRENZ (EFV):

- These are nucleoside unrelated compounds which directly inhibit HIV reverse transcriptase without the need for intracellular phosphorylation.
- Their locus of action on the enzyme is also different, and they are non-competitive inhibitors.
- They are more potent than AZT on HIV-1, but do not inhibit HIV-2. Accordingly, they are not indicated in infections caused by HIV-2.
- If used alone, viral resistance to NNRTIs develops rapidly by point mutation of the enzyme; they should always be combined with 2 other effective drugs.
- Cross-resistance between NVP and EFV is common, but not with NRTIs or PIs. A patient failing any NNRTI regimen should not be treated with another NNRTI.

PHARMACOKINETICS OF NVP & EFV:

- NVP is well absorbed orally; is extensively metabolized, mainly by CYP3A4 and to a lesser extent by CYP2B6, with a t½ of ~ 30 hours.
- Oral absorption of EFV is ~ 50%, but the t½ is longer (48 hours).
- It is completely metabolized, mainly by CYP2B6 and a smaller fraction by CYP3A4.
- Both are enzyme inducers, and cause auto-induction of their own metabolism. However, EFV inhibits CYP3A4 as well.
- Nevirapine is started at a lower dose (200 mg/day); the dose is doubled after 2 weeks when its blood levels go down due to auto-induction.
- Such dose escalation is not required for EFV.
- Rifampin induces NVP metabolism and makes it ineffective, but has little effect on EFV levels.
- If a patient being treated with NVP develops TB and is put on rifampin, NVP should be replaced by EFV.

THERAPEUTICS USES:

- The NNRTIs are indicated in combination regimens for HIV. Either NVP or EFV is included in the first line triple drug regimen used by NACO.
- These drugs have also succeeded in reducing HIV-RNA levels when an earlier regimen (not including an NNRTI) has failed.

ADVERSE EFFECTS:

- **Nevirapine (NVP):** Rashes are the commonest adverse effect, followed by nausea and headache. Occasionally skin reactions are severe. Fever and rise in transaminases occurs dose dependently. NVP is potentially hepatotoxic. In patients developing NVP toxicity, it should be replaced by EFV which has low hepatotoxicity. **NVP should not be used in patients with hepatic dysfunction.**
- **Efavirenz (EFV):** Its side effects are headache, rashes, dizziness, insomnia and a variety of neuropsychiatric symptoms. However, these symptoms decrease over time and discontinuation rate (due to adverse effect) is low. **EFV is contraindicated in pregnancy and in women likely to get pregnant, since it is teratogenic**. Because of its longer plasma t½, occasional missed doses of EFV are less damaging.

RETROVIRAL PROTEASE INHIBITORS (PIS)

- An aspartic protease enzyme encoded by HIV is involved in the production of structural proteins and enzymes (including reverse transcriptase and integrase) of the virus from the large viral polyprotein synthesized in the infected cell.
- The polyprotein is broken into various functional components by this protease enzyme.
- It acts at a **late step in HIV replication**, i.e. maturation of the new virus particles when the RNA genome acquires the core proteins and enzymes.
- Six protease inhibitors:- Atazanavir (ATV), Indinavir (IDV), Nelfinavir (NFV), Saquinavir (SQV), Ritonavir (RTV) and Lopinavir (in combination with ritonavir LPV/r) have been marketed in India for use against HIV.

MECHANISM OF PIS

- They bind to the active site of protease molecule, interfere with its cleaving function, and are more effective viral inhibitors than AZT.
- Because they act at a late step of viral cycle, they are effective in both newly as well as chronically infected cells.
- Under their influence, HIV-infected cells produce immature noninfectious viral progeny hence prevent further rounds of infection.

PHARMACOKINETICS:

- Oral bioavailability of PIs is variable (IDV and RTV ~65%, NFV >20%, SQV 15%) and their plasma t½ ranges from 2–8 hours.
- All are extensively metabolized mainly by CYP3A4, except NFV which is mainly a substrate of CYP2C19.
- All PIs (especially ritonavir and lopinavir) are potent inhibitors of CYP3A4, while some other CYP isoenzymes are induced.
- The PIs interact with many drugs. Nelfinavir, lopinavir and ritonavir induce their own metabolism.

THERAPY:

- In the past monotherapy with one of these drugs in previously AZT treated patients reduced HIV viral levels, increased CD4 cell count and improved the clinical condition.
- However, viral resistance developed against the PIs over months due to selection of resistant mutants in a stepwise manner.
- Combination of NRTIs with PIs has been found more effective than either drug given alone, and triple therapy is more effective than double therapy.
- Current recommendations are to use a PI in combination with either two NRTIs or one NRTI + one NNRTI.
- However, PIs are avoided in 1st line regimens, because their use in initial regimens markedly restricts second line regimen options.
- Most guidelines, including that of NACO, reserve them for failure cases.

ADVERSE EFFECTS:

- The most prominent adverse effects of PIs are gastrointestinal intolerance, asthenia, headache, dizziness, limb and facial tingling, numbness and rashes.
- Of particular concern are lipodystrophy (abdominal obesity, buffalo hump with wasting of limbs and face), dyslipidaemia (raised triglycerides and cholesterol) which may necessitate hypolipidaemic drugs, and insulin resistance.
- Diabetes may be exacerbated.
- Indinavir crystalises in urine and increases risk of urinary calculi.

ANTI-INFLUENZA VIRUS DRUGS

AMANTADINE:

- Chemically, it is a unique tricyclic amine unrelated to any nucleic acid precursor.
- It is active against influenza A virus, but has no action against influenza B virus.

MECHANISM OF ACTION:

- At two stages of viral replication within the host cell, a viral membrane protein M_2, functions as an ion channels.
- The stages are :
  - The fusion of viral membrane and endosome membrane.
  - The later stages of assembly and release of new virions at the host cell surface.
- Amantadine blocks this ion channel.

PHARMACOKINETICS:

- Amantadine is well absorbed orally and excreted unchanged in urine over 2–3 days (t½ 16 hr).

ADVERSE EFFECTS:

- Nausea
- Anorexia
- Insomnia
- Dizziness
- Nightmares
- Lack of mental concentration
- Rarely hallucinations
- Ankle oedema

THERAPEUTIC USES:

- Prophylaxis in influenza A_2
- Parkinsonism

CONTRAINDICATIONS:

- In epilepsy & other CNS ailments.
- Gastric Ulcer
- Pregnancy

ANTI – HEPATITIS VIRUS / NON – SELECTIVE ANTIVIRAL AGENTS

- Several antiviral drugs are relatively virus nonselective and inhibit viruses belonging to different classes; even cover both DNA and RNA viruses.
- While hepatitis B virus (HBV) is a DNA virus which, like retroviruses, can integrate into host chromosomal DNA to establish permanent infection, the hepatitis C virus (HCV) is a RNA virus, which does not integrate into chromosomal DNA, does not establish non-curable infection, but frequently causes chronic hepatitis.

INTERFERON α:

- They are low molecular weight glycoprotein cytokines produced by host cell in response to viral infections and some other inducers.
- There are at least three types: α, β, γ interferon.

MECHANISM OF ACTION:

- It works by inducing in the ribosomes of the host's cells. The production of enzyme that inhibit the translation of viral m – RNA into viral proteins and thus stop the reproduction of the viruses. Interferons bind to specific receptors on cell membranes which may be gangliosides. They inhibit the replication of most viruses *in vitro*.

PHARMACOKINETICS:

- After i.m./s.c. injection, interferon is distributed to tissues. It is degraded mainly in liver and kidney, and remains detectable in plasma for 24 hours.
- They do not cross BBB.

Adverse Effects	Therapeutic Uses
• Fatigue • Malaise • Fever • Dizziness • Visual disturbances • Neurotoxixity • Myelosuppression • Thyroid dysfunction • Hypotension • Transient arrhythmias • Alopecia • Liver dysfunction	• Chronic Hepatitis B & C • AIDS • H. Simplex, H. Zoster, CMV • Rhinoviral (Cold) • Condyloma acumincrta • CML

Thanking You

It is easy to get a thousand prescriptions,
but hard to get one single remedy.