CHEMOTHERAPY OF VIRAL DISEASES-I

NON-RETRO VIRUSES

INTRODUCTION:

- ✓Understanding Viruses: Viruses are different from other Microorganisms. Viruses have no cell wall, Virus Structure is constructed with a Genome: RNA/DNA/never both, a Capsid: Protein shell, an Envelope: Lipoprotein. So, structure of a virus is a Enveloped Capsid containing DNA/RNA.

- ✓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, a copy of its own DNA or RNA.

INTRODUCTION:

- ✓Viral replication: The virus replicative cycle can be divided into 10 steps: (1) adsorption, (2) penetration, (3) un-coating, (4) early transcription, (5) early translation, (6) replication of the viral genome, (7) late transcription, (8) late translation, (9) assembly, and (10) release of new virus particles.

- ✓Examples of virus replication steps controlled by virus-specified enzymes are:- the transcription of positive-sense RNA to DNA (catalysed by the reverse transcriptase associated with retroviruses), the replication of DNA to DNA (catalysed by the DNA polymerases of herpesviruses), and the proteolytic cleavage of viral precursor proteins (catalysed by the protease of human immunodeficiency virus).

INTRODUCTION:

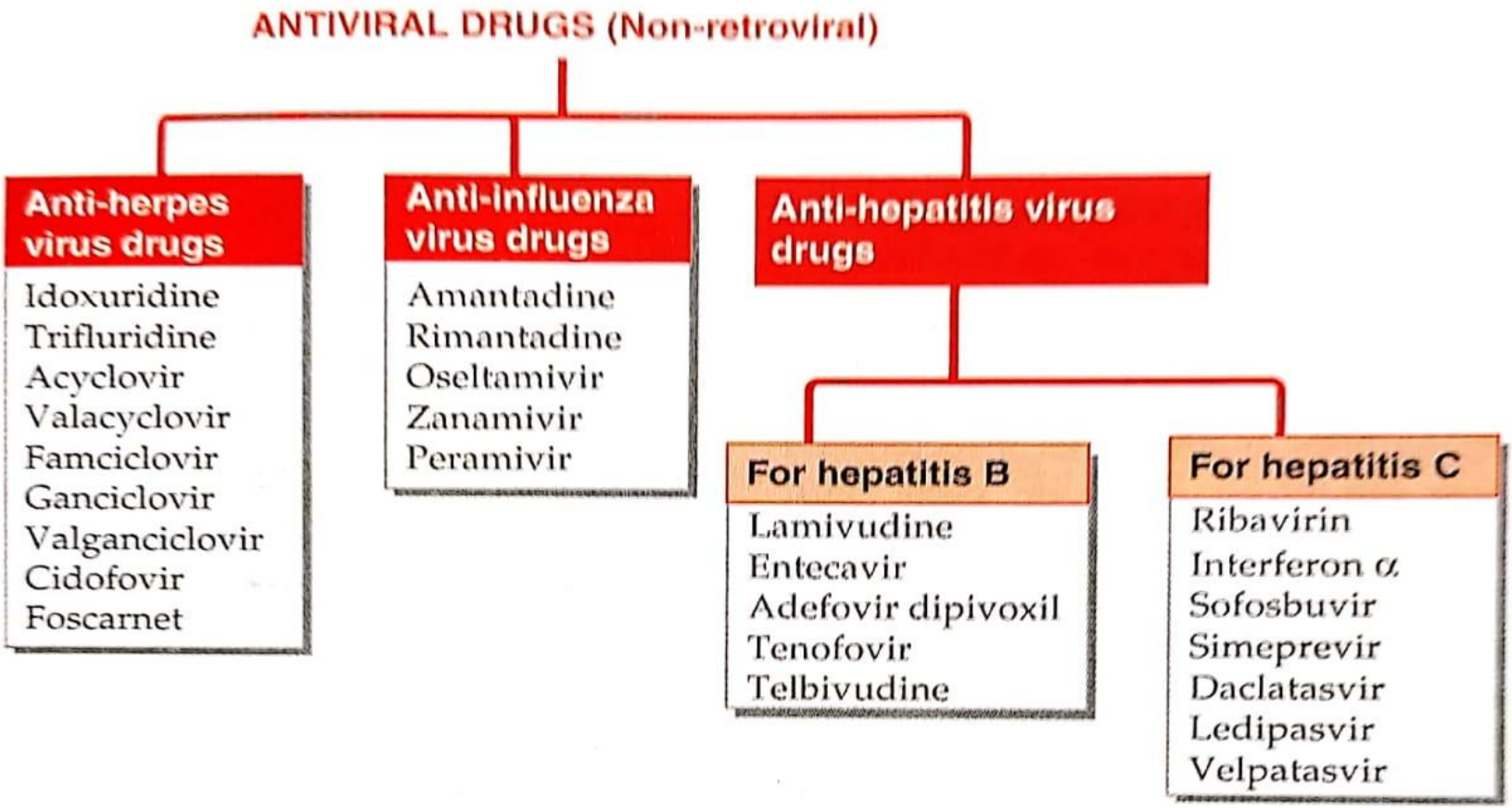
- ✓Antiviral aspect: Viruses are difficult to kill because they live inside the cells. Any drug that kills a virus may also kill host cells.
- ✓Antivirals are available for many viral infections. Viruses controlled by current antiviral therapy are Cytomegalovirus (CMV), Hepatitis viruses, Herpes viruses, Human immunodeficiency virus (HIV), Influenza viruses (the “flu”), Respiratory syncytial virus (RSV) etc.
- ✓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.

Antiviral Medication types:

- ✓Non-retroviral drugs:
- ✓Used to treat non-HIV viral infections:- Influenza viruses; HSV (herpes simplex virus); VZV (varicella zoster virus); CMV (cytomegalovirus); Hepatitis A, B, C (HAV, HBV, HCV).
- ✓Mechanism of action: Inhibit viral replication.
- ✓Adverse Effects: Vary with each drug ⁄ Healthy cells are often killed also, resulting in serious toxicities.
- ✓Current anti-viral agents do not eliminate non-replicating or latent virus. Effective host immune response remains essential for the recovery from the viral infection.

- ✓Antiretroviral drugs:
- ✓Used to treat infections caused by HIV.

CLASSIFICATIONS:



ANTI-HERPES VIRUS DRUG:

- **Idoxuridine and Trifluridine**
- Because of their myelosuppressive, mutagenic and teratogenic effects after systemic administration, idoxuridine and trifluridine are only suitable for topical use. Trifluridine is superior to idoxuridine when used in eyedrops for the topical treatment of herpetic keratitis. Idoxuridine can be formulated for topical treatment of herpetic skin lesions.

ANTI-HERPES VIRUS DRUG:

- **Acyclovir, Valaciclovir and Famciclovir**
- Acyclovir represents a major breakthrough in the treatment of herpesvirus infections.
- Mechanism of action: Acyclovir and congeners are phosphorylated by a viral thymidine-kinase, then metabolized by host cell kinases to nucleotide analogues. The analogue inhibits viral DNA- polymerase. Only actively replicating viruses are inhibited
- Indications for its use are primary genital herpes, herpetic encephalitis and herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections in immunosuppressed patients.
- It can be used topically, intravenously, or orally, although its oral absorption is only 20 percent. It offers limited benefit in the topical treatment of recurrent herpes labialis. It is also efficacious in preventing recurrent genital herpes, as well as in preventing HSV infections in renal allograft recipients.

ANTI-HERPES VIRUS DRUG:

- ✓**Acyclovir, Valaciclovir and Famciclovir**
- ✓Based on an alteration of their thymidine kinase, HSV and VZV may develop resistance to acyclovir, particularly in immunocompromised patients.
- ✓Valaciclovir and Famciclovir represent two orally bioavailable compounds for the treatment of HSV and VZV infections.
- ✓Their main indication is herpes zoster.
- ✓Valaciclovir and famciclovir act as prodrugs of acyclovir and penciclovir, respectively.
- ✓Penciclovir acts in a similar fashion as acyclovir, although it would generate higher intracellular levels of the triphosphate form, which is supposed to be the active metabolite for these compounds.

ANTI-HERPES VIRUS DRUG:

- **Ganciclovir, Foscarnet**
- Ganciclovir is the preferred drug for treating cytomegalovirus (CMV) infections in patients with acquired immune deficiency syndrome (AIDS) or other immunodeficiencies but also inhibits other herpes viruses(HSV, HZV & EBV). It has very poor oral bioavailability (3 percent), and, therefore, mostly given intravenously. Of the various clinical manifestations of cytomegalovirus infection in immunosuppressed patients, cytomegalovirus retinitis responds best to ganciclovir therapy, but recurs after treatment is stopped. The most frequent adverse side effects are granulocytopenia (neutropenia) and thrombocytopenia.

- Foscarnet is the second drug used in the treatment of CMV infections, particularly CMV retinitis, in immunocompromised patients. It must be given intravenously, and it has proved effective in delaying progression of CMV retinitis compared to untreated controls.

ANTI-INFLUENZA VIRUS DRUG:

- **Amantadine and Rimantadine**
- The clinical use of Amantadine and Rimantadine is restricted to the prophylaxis and early therapy of influenza A virus infections. Influenza prophylaxis is particularly indicated in immuno-deficient patients, persons who are allergic to influenza vaccine, unvaccinated house contacts of high-risk patients, and residents of chronic care facilities where an outbreak of influenza A has been recognized.
- Side effects: Amantadine is noted for its central nervous system side effects, such as hallucinations and disorientation, which lead, for example, to a risk of falling.
- Rimantadine causes fewer side effects than amantadine, when used at the same dosage (200 mg/day, per orally).

ANTI-INFLUENZA VIRUS DRUG:

- **Oseltamivir**
- It is the most commonly used anti-influenza virus drug. It is a sialic acid analogue with broad spectrum activity covering influenza-A, H5N1(bird flu), H1N1(Swine flu) and influenza-B.
- Mode of Action: It acts by inhibiting influenza virus neuraminidase enzyme which is needed for release of progeny virions from the infected cell.
- Side effects: Nausea and abdominal pain due to gastric irritation, headache, weakness, sadness, diarrhoea, cough and insomnia.
- Dose: Therapeutic- 75mg oral BD for 5 days; prophylactic- 75mg OD.
- **Zanamivir**
- Administered by inhalation as a powder due to very low oral bioavailability. The MOA, indication & efficacy are similar to oseltamivir.

ANTI-HEPATITIS-B VIRUS DRUG:

- ✓**Lamivudine**
- ✓This nucleoside analogue is active against HBV as well as HIV.
- ✓Mode of Action: This deoxycytidine analogue is phosphorylated intracellularly and inhibits HIV reverse transcription as well as HBV DNA polymerase.
- ✓Resistance: Its incorporation into viral DNA results in termination. Most human DNA polymerases are not affected, so systemic toxicity is low. But point mutation in HBV DNA polymerase gives rise to rapid lamivudine resistance.
- ✓**Entecavir**
- ✓This guanosine nucleoside analogue is currently the most active and 1st line option for treating chronic hepatitis-B
- ✓Mode of Action: Entemivir inhibits HBV DNA polymerase after activation by intracellular phosphorylation.

ANTI-HEPATITIS-B VIRUS DRUG:

- ✓**Entecavir**
- ✓Entemivir is nearly completely absorbed after oral dosing, but food decreases bioavailability, so it should be taken in empty stomach.
- ✓It is not metabolised and excreted unchanged through kidney with a $t_{1/2}$ of 128-148hrs.
- ✓Side Effects: mild dyspepsia, nausea, diarrhoea, fatigue and disturbed sleep.
- ✓Dose: 0.5mg OD, for resistant cases- 1mg OD.
- ✓**Adefovir dipivoxil**
- ✓It is a mono-phosphate analogue of AMP, active against hepatitis caused by HBV. It is least active nucleotide analogue against HBV, so it is not a 1st line drug.
- ✓Mode of Action: On entering cells, adefovir is phosphorylated to the diphosphate which has high affinity for HBV DNA polymerase compared to host cell DNA polymerase and get incorporated into viral DNA resulting in termination of viral DNA chain.
- ✓Dose: 10mg/day.

ANTI-HEPATITIS-B VIRUS DRUG:

- ✓**Tenofovir disoproxil fumarate (TDF)**
- ✓It is a monophosphate nucleotide related to AMP, having poor oral absorption so, it is used as disoproxil ester prodrug.
- ✓Mode of Action: Tenofovir released from hydrolysis of prodrug is dephosphorylated by cellular kinase into tenofovir diphosphate which preferentially inhibits HBV DNA polymerase.
- ✓Side Effects: nausea, flatulence, abdominal discomfort, loose motion and headache.
- ✓Dose: 300mg OD.
- ✓**Telbivudine**
- ✓It is a thymidine nucleoside analogue. It is absorbed orally and its bio availability is not affected by food. Not metabolised and excreted unchanged by kidney.
- ✓Mode of Action: On entering cells, it is phosphorylated to the triphosphate which competetively inhibits HBV DNA polymerase. Dose: 600mg/day.

ANTI-HEPATITIS-C VIRUS DRUG:

- **Ribavirin**
- Although active against HCV, influenza A, B, ortho- and paramyxoviruses, ribavirin is approved only for the treatment of respiratory syncytial virus (RSV) infection in infants. The drug is administered as a small-particle aerosol (particle diameter, 1 to 3 μm) so that it can reach the lower respiratory tract. Aerosolized ribavirin treatment results in more rapid cessation of viral shedding and resolution of clinical symptoms without signs of systemic toxicity.
- **Interferon Alpha**
- It is low molecular weight glycoprotein cytokines. Interferons inhibit many RNA & DNA viruses, but they are host specific, those produced by another species have poor activity in man.
- Side Effect: Flu like symptom, neurotoxicity, myelosuppression.

ANTI-HEPATITIS-C VIRUS DRUG:

- ✓**NS5B polymerase inhibitor (Sofosbuvir)**
- ✓It is active against all (1-6) HCV genotypes, especially genotype 1, but always used in combination with NS5A inhibitors or simeprevir or ribavirin.
- ✓Mode of Action: Uridine analogue prodrug, in hepatic cells, it is phosphorylated to the triphosphate nucleotide and inhibits HBV non-structural protein 5B (NS5B) which is a HCV RNA polymerase.
- ✓Oral bioavailability is 80% and is improved if taken with fatty meal.
- ✓Interactions: Can't be used with Pgp inducers like phenytoin, rifampin and patient having renal impairment.
- ✓Dose: 400mg/day with meal.

ANTI-HEPATITIS-C VIRUS DRUG:

- ✓**NS3/4A protease inhibitor (Simeprevir)**
- ✓It is active against (1&4) HCV genotypes and recommended to use with NS5A inhibitors or ribavirin + PegINF$_{alpha}$.
- ✓Mode of Action: It is a HCV protease NS3 inhibitor which blocks the cleavage of HCV polyprotein complex, so that functional viral RNA is not formed.
- ✓Interactions: Significant clinical interactions with rifampin, statins and protease inhibitor antiretroviral drugs.
- ✓Dose: 150mg/day.
- ✓**NS5A inhibitors (Daclatasvir)**
- ✓It is active against all (1-6) HCV genotypes.
- ✓Mode of Action: It is an orally active NS5A inhibitor which blocks HCV RNA replication.
- ✓Dose: 60mg/day.

Very Very Viral