ANTIVIRAL DRUGS

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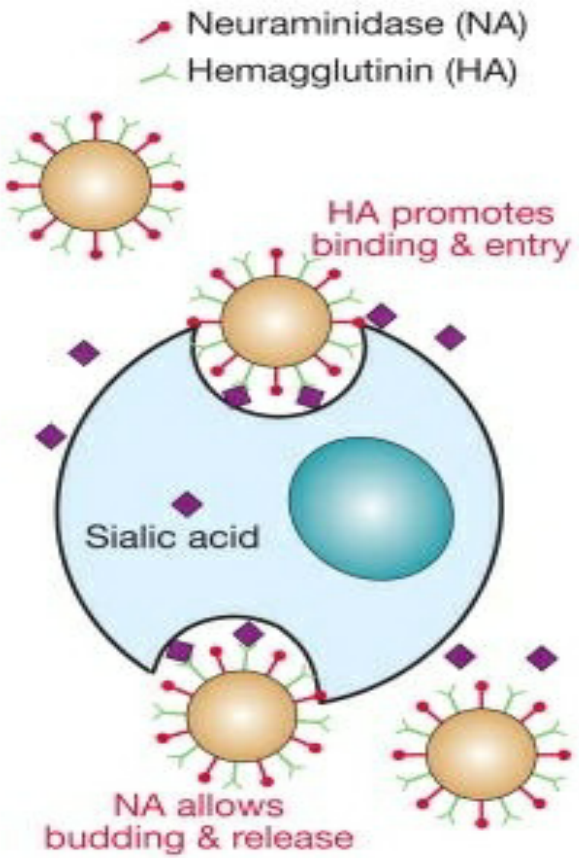
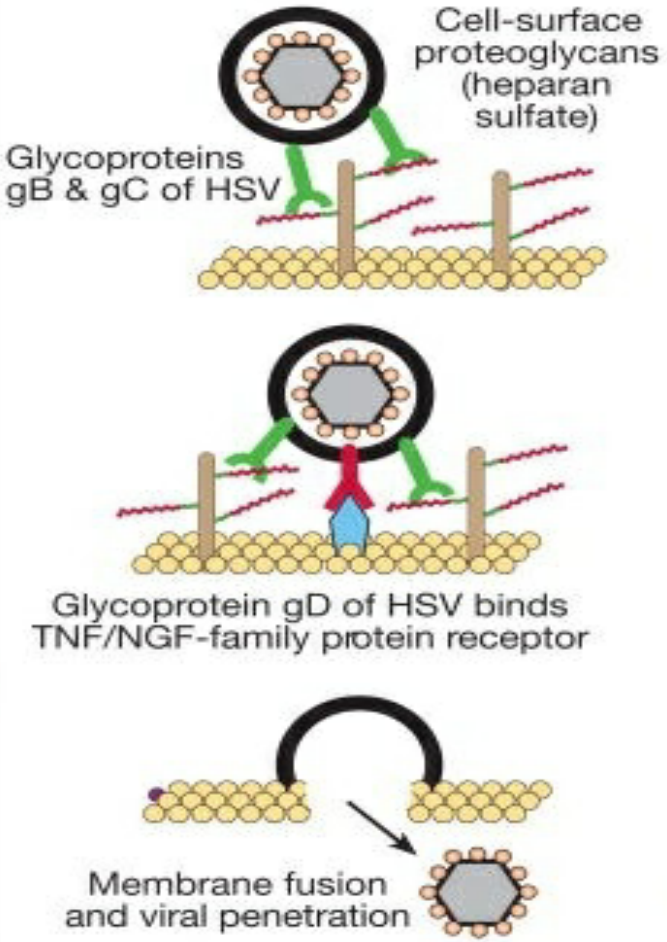
INTRODUCTION

- Viruses present more difficult problem of chemotherapy than do other higher organisms e.g bacteria for they are intracellular parasites that use the metabolism of host cells.
- They also share metabolic processes of the host cell
- Identification of the difference between human and viral metabolism, however, has led to the development of effective antiviral agents

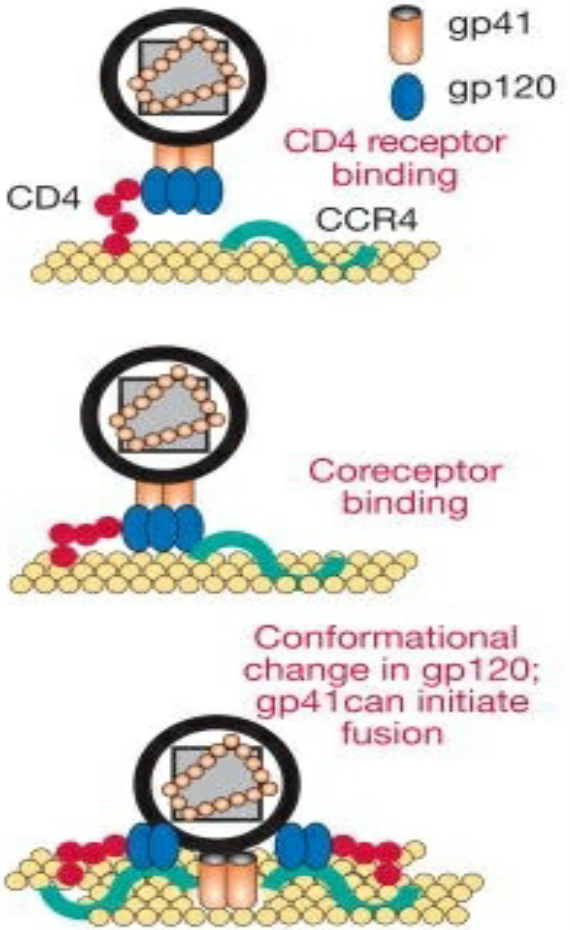
a) Influenza Viruses



b) Herpes Simplex Virus



c) HIV/AIDS Virus



CLASSIFICATION OF ANTIVIRAL DRUGS

- There are two classes of antivirals

Drugs that directly impair virus replication

- Nucleoside reverse transcriptase inhibitors
- Nucleotide reverse transcriptase inhibitors
- Non-nucleoside reverse transcriptase inhibitors
- Protease inhibitors
- Fusion inhibitors
- Integrase inhibitors
- CCR5 Antagonists
- DNA polymerse inhibitors
- Inhibitors of viral coat disassembly and neuraminidase/ ant-influenza drugs

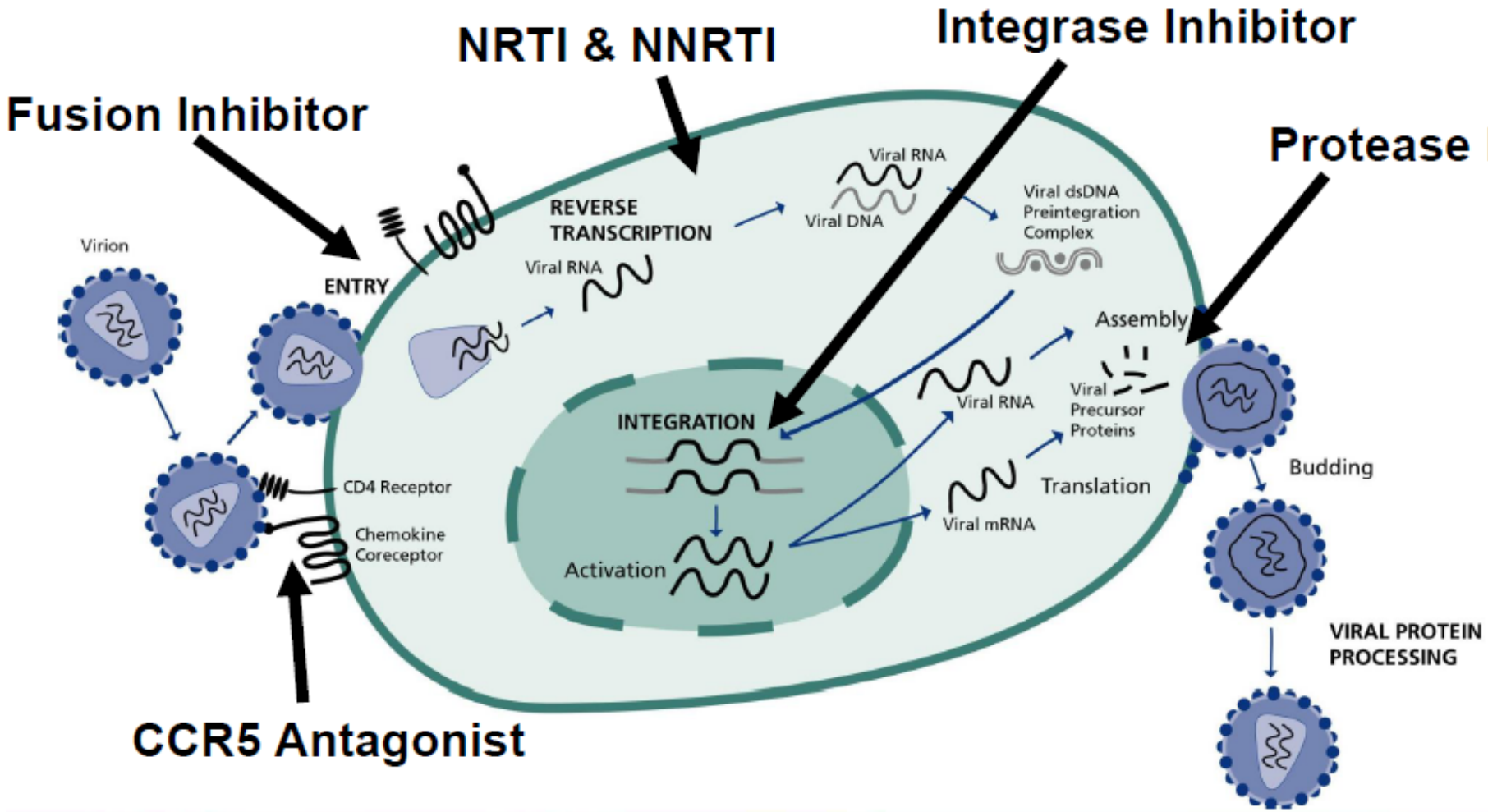
Drug that modulate host immune system

- Immunoglobulin
- interferon

ANTIVIRALS: CLASSIFICATIONS

v • d • e	Antivirals (primarily J05A, also S01AD and D06BB)
Anti-herpesvirus	Aciclovir, Cidofovir, Docosanol, Famciclovir, Fomivirsen, Foscarnet, Ganciclovir, Idoxuridine, Penciclovir, Trifluridine, Tromantadine, Valaciclovir, Valganciclovir, Vidarabine
Anti-influenza agents	Amantadine, Arbidol, Oseltamivir, Peramivir, Rimantadine, Zanamivir
Antiretrovirals: NRTIs	Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Zalcitabine, Zidovudine
Antiretrovirals: NtRTIs	Tenofovir
Antiretrovirals: NNRTIs	Efavirenz, Delavirdine, Nevirapine, Loviride
Antiretrovirals: PIs	Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir
Antiretrovirals: Fusion inhibitors	Enfuvirtide
Other antiviral agents	Adefovir, Fomivirsen, Imiquimod, Inosine, Interferon, Podophyllotoxin, Ribavirin, Viramidine

HIV Life Cycle & ARV Action Sites



CLASSIFICATION: DRUGS THAT DIRECTLY IMPAIR VIRAL REPLICATION

Nucleoside reverse transcriptase inhibitors (NRTI)

- This classs include: zidovudine (AZT), abacavir (ABC), lamivudine (3TC), didanosine (ddI), zalcitabine (ddC), stavudine (D4t) and Emtricitabine.

Mechanism of action

- All are phosphorylated by host cell enzyme to give 5'-triphosphate. The 5'-triphosphate moiety competes with equivalent host cellular triphosphate , which are essential substrates for the formation of proviral DNA by viral reverse transcriptase (viral RNA –dependent DNA polymerse); the incorporation of 5;-triphosphate moiety into the growing viral DNA results in chain termination.

NRTI

1. **Zidovudine (AZT)**

- It is an analogue of thymidine

Indication

- Serous manifestation of HIV in patients with AIDS or AIDS related complex
- Early symptomatic and asymptomatic HIV infections when blood markers indicate risk of disease progression

Available dosage forms:

- Oral: 100 mg capsules, 300 mg tablets, 50 mg/5 ml syrup
- Parenteral: 10mg/ml injection

Dose: adult; 300 mg bd

Interactions

- Increased serum level occurs with concomitant administration with probenecid, phenytoin, methadone, fluconazole, artovaquone, valproic acid and lamivudine either through inhibition of first pass metabolism or decreased clearance. Zidovudine may decrease serum phenytoin levels

NRTI CONT

Adverse effects of zidovudine

- Common; myelosuppression resulting in anemia or neutropenia
- GIT diturbances- nausea , vomiting
- Headaches and insomnia
- Uncommon; thrombocytopenia, hyperpigmentation of nails, myopathy, fatal lactic acidosis and severe hepatomegaly
- High doses can cause anxiety, confusion and tremulousness

Management of ADR (Adverse Drug Reaction)

- Drug withdrawal incase of anemia/change of regimen
- Folic acid and ferrous sulphate for anemia; transfuse whole blood if severe

Contraindications

- Anemia
- Myelosuppressive disorders
- Hypersensitivity to zidovudine

Precautions

- Administered with caution in patients taking anticancer agents and other drugs causing bone marrow depression

NRTI CONT

Metabolism, half life and excretion

- Bioavailability is 60-80% and the peak plasma concentration occurs at 30 minutes. Its half life is 1 hour and intracellular half life of active triphosphate is 3 hours
- Most of the drug is metabolized to the inactive glucuronide in the liver, only 20% of the active form being excreted in urine.

NRTI CONT

2. Didanosine (ddi)

- It is a synthetic analogue of deoxyadenosine
- **Indication**: HIV infection
- **Available dosage forms**: oral; 25,50,100, 150 mg tablets, 100, 167, 250, 375 mg powder for oral solution, 2.4 g powder for pediatric solution
- **Dose** : p.o capsule 250-400mg daily, depending on weight, tablet/capsules: 125-250 mg bd depending on weight. Adjust dose in renal insufficiency

Adverse effects

- Peripheral neuropathy, pancreatitis, diarrhea, hyperuricemia, GIT disturbances, headache. Others: insomnia, skin rashes, bone marrow depression (less marked) and alteration of liver function tests.

NRTI CONT....

Management of ADR

- Peripheral neuropathy; p.o pyridoxine 50 mg od

Contraindications

- Alcoholism
- Hypertriglyceridemia
- Pancreatitis
- Drugs with potential to cause pancreatitis and peripheral neuropathy
- Gout/hyperuricemia

Interactions

- Food interferes with absorption
- Interferes with absorption of ketoconazole, itraconazole and dapsone
- It chelates tetracyclines and itraconazole
- Ganciclovir increases absorption
- Methadone interferes with absorption

Precautions

- Tablet contains phenylalanine and sodium , caution should be exercised in patients with phenylketonuria and on sodium restricted diet. Dosage reduction in low creatinine clearance, after hemodialysis and low body weight.

NRTI CONT

Metabolism, excretion and half life

- Elimination half life is 0.6-1.5 hours, but intracellular half life of activated compound is 12-24 hours
- The drug is eliminated by glomerular filtration and tubular secretion

3. Lamivudine (3TC)

- It is a cytosine analogue
- **Indication:** HIV infection, HBV infections
- **Available dosage forms:** oral: 100, 150 mg tablets, 10mg/ml oral solution. Oral (combivir) 150 mg tab in combination with zidovudine 300 mg
- **Dose:** 150 mg bd or 300 mg od daily depending on weight
- **Interactions**: nelfinavir increases serum concentration of lamivudine, abacavir, tenofovir and nevirapine reduces its serum concentration. Cotrimoxazole increases bioavailability of lamivudine

NRTI CONT..

Adverse effects

- Lamivudine has excellent safety profiles. Headache, nausea, insomnia and dizziness are rare

Contraindications

- Patients on zalcitabine (inhibits intracellular phosphorylation of lamivudine)

Metabolism and excretion

- Well absorbed and excreted in urine unchanged
- Mean elimination half life is 2.5 hours, intracellular half life of active metabolite in HIV infected cell line is 10.5-15.5 hours and HBV cell line is 17-19 hours

NRTI CONT

4. ZALCITABINE (ddC)

Indications

- Used against zidovudine sensitive and zidovudine resistant strain of HIV-1

Available dosage forms: oral: 0.375 mg, 0.75 mg tablets

Dose: 0.75 mg tid

Interactions

- Probenecid and cimetidine increases AUC of zalcitabine
- Antacids and metoclopramide decreases bioavailability
- Lamivudine inhibits its phosphorylation and interferes with efficacy

Adverse effects

- Dose dependent peripheral neuropathy
- Oral and esophageal ulcerations
- Pancreatitis
- Mild headache,nausea, rash and arthralgia
- Cardiomyopathy. rare

NRTI CONT…

Management of ADRs

- Dose reduction to prevent peripheral neuropathy
- Use pyridoxine 50 mg od

Contraindications

- Other drugs that may cause neuropathy such as stavudine, didanosine and isoniazid
- Patients taking amphotericin B, foscarnet and aminoglycosides may increase risk of neuropathy since they decrease renal clearance of zalcitabine

Metabolism and excreation

- Zalcitabine has relatively longer half-life of 10 hours and high oral bioavailability of > 80%
- Eliminated in the kidneys

NRTI CONT

5. STAVUDINE (D4t)

Indications

- HIV infections
- **Available dosage forms:** oral: 15,20,30,40 mg capsules; powder for 1 mg/ml oral solution
- **Dose:** 30-40 mg bd, depending on the weight

Adverse effects

- Neuropathy
- Arthralgia
- Pancreatitis
- Serum elevation of aminotransferase
- Lipodystrophy

Management of ADRs

- Pyridoxine 50 mg od for neuropathy

Contraindications

- Patients on neuropathic inducing drugs such as zalcitabine , isoniazid and didanosine

NRTI CINT…

Precautions

- Dosages should be reduced in patients wit renal insufficiency, those receiving hemodialysis and for low body weight

Metabolism, half-life and excretion

- Plasma half life is 1.22 hours; intracellular half life is 3.5 hours
- Excretion is by active tubular secretion and glomerular filtration
- High oral bioavailability, 80% that is not food dependent

6. **ABACAVIR (ABC)**

It's a guanosine analogue

Indications

- HIV infections in combination with other antiretrovirals
- **Available dosage form**s: oral: 300 mg tablets, 20 mg/ml solution. Oral (Trizir): 300 mg tablets in combination with lamivudine 150 mg and 300 mg zidovudine
- **Dose:** 300 mg bd

NRTI CONT…

Adverse effects

- Hypersensitivity reactions 2-5%
- Fever, malaise and GIT complaints occurs within first 6 weeks of therapy
- Rash
- Nausea, vomiting and diarrhea
- Headache and fatigue
- Pancreatitis, rare
- Hyperglycemia, rare
- Hypertriglyceridemia, rare

Management of ADRs

- Withdraw the drug in case hypersensitivity reaction is reported
- Give corticosteroids (hydrocortisone/prednisolone) and antihistamine

Interactions: coadministration with alcohol increases abacavir's AUC

Half-life, metabolism and excretion

- Elimination half life is 1.5 hours
- Metabolized by alcohol dehydrogenase and glucuronyl transferase to inactive metabolites that are eliminated primarily in the liver

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS NtRTI

TENOFOVIR (TDF)

- Tenofovir disoproxifumarate is a pro drug that is converted in vivo to tenofovir, an acyclic nucleoside phosphate (nucleotide) analogue of adenosine

Mechanism of action

- Competitively inhibits HIV reverse transcriptase and causes chain termination after incorporation of DNA.

Indications

- HIV infection together with other antiretrovirals

Available dosage forms: 300 mg tablets

Dose: 300 mg od

Interactions

- Food (fatty meal) increases oral bioavailability
- Not metabolized by CYP450 thus minimal drug interactions
- Compete with other drugs that are excreted by the kidneys e.g. cidofovir, acyclovir and ganciclovir

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR

Adverse effects

- GIT effects; nausea, vomiting, diarrhea and flatulence, nephrotoxicity.
- **Precautions**: watch for lactic acidosis and hepatomegaly

Pharmacokinetics

- Bioavailability is increased if the drug is ingested following a high fatty meal
- Maximum serum concentrations are achieved in about 1 hour after taking medications
- Elimination occurs by a combination of glomerular filtration and active tubular secretions
- However , only 70-80% of the dose recovered in the urine, allowing for possibility of hepatic metabolism as well as alteration in hepatic insufficiency

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS, NNRTI

- This class include: nevirapine (NVP), delavirdine and efavirenz (EFV)

1. **NEVIRAPINE**

Indications

- HIV infection as a component of antiretroviral regimen

Available dosage forms:oral: 200 mg tablets, 50 mg/5 ml suspension

Dose: 200 mg bd; gradual dose escalation over 14 days is recommended to decrease frequency of rash i.e. 200 mg od for first 14 days

Interactions

- Nevirapine is both a substrate and a moderate inducer of CYP3A metabolism resulting in 1.5 to 2 fold increase in oral clearance of itself and decreased levels of indinavir and saquinavir if administered concurrently

NnRTI CONT….

- Nevirapine levels may increase during coadministration with inhibitors of CYP3A metabolism such as cimetidine and a macrolide agent and decrease in presence of CYP3A inducers such as rifabutin and rifampicin.
- Nevirapine reduces levels of ketoconazole on coadministration as it levels increases

Contraindication

- Patients on ketoconazole, methadone and oral contraceptives
- Hypersensitivity to nevirapine
- Patients with severe rash

Precautions: Dose escalation from 200 od over 14 days to decrease frequency of rash

Adverse effects

- Severe life threatening skin rashes have occurred during nevirapine therapy including Steven Johnson syndrome and toxic epidermal necrosis
- Fulminant hepatitis and fever
- Nausea, headache and somnolence

NnTI CONT.....

- **Management of ADRs**
- Withdraw the drug incase of rash (change to other regimen)
- Use corticosteroids (hydrocortisone/prednisolone) and antibiotics(cephalosporins, penicillins) to manage Steven Johnson syndrome and toxic epidermal necrosis

Pharmacokinetics

- Oral bioavailability of nevirapine is excellent (>90%) and is not food dependent
- The drug is highly lipophilic and about 60% is protein bound
- It is extensively metabolized by CYP3A isoform to hydroxylated metabolites and then excreted primarily in urine

NnRTI CONT……

2. DELAVIRDINE

Indications

- HIV infections in combination with other antiretrovirals
- Available dosage forms: oral: 100. 200 mg tablets

Dose: 400 mg tid

Interactions

- Delavirdine plasma concentrations are reduced in presence of antacids, phenytoin, phenobarbital, carbamazepine, rifabutin, , didanosine, rifampicin and nelfinavir
- Delavirdine serum concentrations is increased during coadministration with clarithromycin,fluoxetine, dexamethasone, saquinavir and ketoconazole.

Adverse effects

- Skin rash; occur in about 18% of patients, however not severe
- Headache, fatique, nausea and diarrhea
- Increased serum aminotransferase
- Teratogenic in rats causing ventricular septal defects

NnRTI CONT....

Contraindications

- Pregnancy

Precautions

- Caution should be used when administering delavirdine to patients with hepatic insufficiency because clinical experience in this situation is limited

Pharmacokinetics

- Oral bioavailabilty of 85% but this is reduced by antacids
- About 98% is bound to plasma proteins
- Extensively metabolized in the liver by CYP3A and CYP2D6 enzymes; however, it also inhibits CYP3A and thus inhibits its own metabolism

NnRTI CONT.....

3. _EFAVIRENZ

Indications

- HIV infections in combination with other antiretrovirals
- **Available dosage forms:** oral: 50,100,200 mg capsules; 600 mg tablets

Dose:600 mg od

Interactions

- Efavirenz is a substrate, an inhibitor and a moderate inducer of CYP3A4 thus inducing its own metabolism and interacting with many drugs
- Agents that induce CYP3A4 decreases plasma concentrations of efavirenz e.g. phenobarbitone, rifampicin and rifabutin
- Efavirenz reduces plasma levels of clarithromycin, methadone, saquinavir and indinavir but increases plasma levels of ethinylestradiol.
- High fat meal increases bioavailability by 65%

NnRTI CONT.....

Adverse effects

- CNS effects: dizziness, drowsiness, insomnia, headache, confusion, amnesia, agitation, delusions, depression, nightmares and euphoria
- Mild to moderate skin rash
- Nausea, vomiting and diarrhea
- Crystalluria
- Elevated liver enzymes
- Increase in total serum cholesterol by 10-20%

Contraindications

- Hypercholesterolemia
- Hyperlipidemia

NnRTI CONT….

Pharmacokinetics of efavirenz

- Has a long half life of 40-55 hours
- Peak plasma concentrations are seen 3-5 hours after administration; steady state plasma concentrations are reached in 6-10 days.
- Efavirenz is principally metabolized by CYP3A4 and CYP2B6 to inactive hydroxylated metabolites; the remainder is eliminated in feces as unchanged drug.

PROTEASE INHIBITORS, PIs

- This class include; Saquinavir, ritonavir, lopinavir,indinavir, nelfinavir, amprenavir and atazanavir

Mechanism of action

- During the later stages of the HIV growth cycle, the *Gag* and *Gag-Pol* gene products are translated into polyproteins, and these become immature budding particles. Protease is responsible for cleaving these precursor molecules to produce the final structural proteins of the mature virion core. By preventing cleavage of the Gag-Pol polyprotein, protease inhibitors (PIs) result in the production of immature, noninfectious viral particles . Unfortunately, specific genotypic alterations that confer phenotypic resistance are fairly common with these agents, thus contraindicating monotherapy.

PIs cont…

1. RITONAVIR

Indication

- HIV infections in combination with other antiretrovirals
- **Available dosage forms:** oral: 100 mg capsules; 80 mg/ml oral solution
- **Dose**: 600 mg bid

Interactions

- Its an inhibitor of CYP3A4 and therefore concurrent administration with other PIs results in increased plasma levels of latter drugs
- Delavirdine and efavirenz increases plasma levels of ritonavir while didanosine, indinavir and zidovudine will decrease its serum concentrations

Adverse effects

- GIT disturbances e.g. diarrhea
- Paresthesias (circumoral and peripheral)
- Elevated serum aminotransferases
- Altered taste
- Hypertriglyceridemia
- Nausea, vomiting and abdominal pain

PIs cont….

Precautions

- Caution is advised when administering the drug to patients with impaired hepatic function

Pharmacokinetics

- Metabolism to an active metabolite occurs via the CYP3A and CYP2D6 isoforms
- Excretion is primarily in the feces
- Bioavailability is about 75% that increases when the drug is given with food

PIs cont…

2. LOPINAVIR/RITONAVIR (Kaletra, Alluvia)

- Several studies have shown enhanced efficacy or improved tolerability if two PIs are administered together
- Lopinanavir 200 mg/ritonavir 50 mg is a licensed combination in which subtherapeutic doses of ritonavir inhibits CYP3A4 mediated metabolism of lopinavir, thereby resulting in increased exposure to lopinavir

Indications

- HIV infection in combination with other antiretrovirals; it mantains potent viral suppression and provide pharmacological barrier to emergency of resistance
- **Adult Dose**: 400mg/100mg bd

Interactions

- Food enhances absorption
- Coadministration with rifampicin, carbamazepine, phenobarbital, phenytoin, dexamethasone or St John's wart (*hypericum perforatum*) may reduce levels of lopinavir
- Delavirdine and ritonavir increases serum level of lopinavir

Adverse effects

- Diarrhea, abdominal pain, nausea, vomiting and asthenia.

PIs cont…

Pharmacokinetics

- Absorption is enhanced with food
- Lopinavir is 98-99% protein bound and is extensively metabolized by the CYP3A4 isoenzyme, which is inhibited by ritonavir.
- Serum levels of lopinavir may be increased in patients with hepatic impairment.

PIs cont…

3. ATAZANAVIR

- Atazanavir is a newer azapeptide PI with a pharmacokinetic profile that allows once-daily dosing. Its oral bioavailability is approximately 60–68%; the drug should be taken with food. The plasma half-life is 6–7 hours, which increases to approximately 11 hours when co-administered with ritonavir. The primary route of elimination is biliary; atazanavir should not be given to patients with severe hepatic insufficiency.
- The most common adverse effects: nausea, vomiting, diarrhea, abdominal pain, headache, peripheral neuropathy, and skin rash
- As an inhibitor of CYP3A4 and CYP2C9, the potential for drug-drug interactions with atazanavir is great. Atazanavir AUC is reduced by 76% on average when combined with omeprazole; thus, the combination is to be avoided. In addition, co-administration with other drugs that inhibit the glucuronidation enzyme UGT1A1, such as indinavir and irinotecan, is contraindicated. Tenofovir and efavirenz should not be co-administered with atazanavir unless ritonavir is added to boost levels.

FUSION INHIBITORS

ENFURVITIDE

Mechanism of action

- Blocks entry of virus into the cell
- It binds to gp14 sub unit of the viral envelop glycoprotein, preventing conformational changes required for fusion of viral and cellular membranes

Indications

- Treatment of patients with persistent HIV-1 replication despite ongoing therapy
- **Avaialble dosage forms:** Parenteral; 90 mg/ml for injection
- **Dose:** 90 mg bid subcutaneously
- **Interactions:** no interactions has been reported to date

Adverse effects

- Local injection site reactions (most common ADR)
- Hypersensitivity reactions
- Eosinophilia

FUSION INHIBITOR

Pharmacokinetics

- Protein binding is high (about 90%) and metabolism appears to be by proteolytic hydrolysis without involvement of cytochrome P450 systems
- Elimination half life is 3.8 hours
- Time to peak concentrations is 8 hours

Integrase inhibitors

- Include Dolutegravir and Raltegravir
- **DOLUTEGRAVIR**

Benefits of DTG

- It is better tolerated
- Has higher antiretroviral potency
- Achieves faster viral suppression
- Has a high genetic barrier for resistance
- It is available in fixed dose combination as TDF/3TC/DTG (TLD)
- Has fewer drug-to-drug interactions

Drug interactions

- Significant drug interactions
  a) Rifampin: use DTG 50 mg BD
  b) Rifabutin: no dose adjustment required
  c) Antacids and multivitamins/minerals: Administer DTG at least 2 hours before or 6 hours after taking supplements or antacids containing Mg, Al, Fe, Ca and Zn. For Ca or Fe, if DTG is taken with a meal then dose separation is not required
  d) Metformin: use lower dose of metformin and monitor glycemic control
  e) Anti-seizure medications: consult, may need alternative anticonvulsants
- Contraindications
  a) Hypersensitivity to DTG
  b) End-stage renal disease; end-stage liver disease (not studied)

Adverse effects

- Generally well tolerated
- Most common AEs are insomnia, headache, nausea, diarrhea
- CNS AEs are common in older age (> 60 years) , co-administration with ABC, and higher plasma drug levels
- Insomnia **may** improve if administered with low-fat meal or on an empty stomach (theoretical)

Note: Advise patient to take DTG in the morning and preferably with low fat diet to minimize the AEs

CCR5 ANTAGONISTS

MARAVIROC

- Indications

➤ Combination antiretroviral treatment of CCR5 tropic HIV-1 in patients who have viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

➤ Dosage differs based on concomitant medications owing to drug interactions. Ranges from 150mg bd to 600mg bd

MOA

- Selective antagonist of the interaction between human CCR5 and HIV-1 gp120. blocking this interaction prevents CCR5-tropic HIV-1 entry into cells.

pharmacokinetics

- Bioavailability is 23-33%
- Protein binding is 76%
- Metabolised by cytochrome P450 system, with CYP3A as major enzyme of metabolism.
- 76% excreted through feces and 20% through urine.

Contraindications

- Concomitant administration with emtricitabine, tenofovir DF
- Hypersensitivity

Adverse effects

- Upper respiratory infections
- Arthritis and musculoskeletal
- Cough
- Pyrexia
- Rash
- Fever

DNA POLYMERASE INHIBITORS

- This class include: acyclovir, cidofovir, famciclovir, foscarnet, ganciclovir, idoxuridine and penciclovir

1. **ACYCLOVIR**

- Its acyclic guanosine derivative with clinical activity against HSV-1, HSV-2 and varicella zoster virus

Mechanism of action

- Acyclovir requires three phosphorylation steps for activation. It is converted first to the monophosphate derivative by the virus-specified thymidine kinase and then to the di- and triphosphate compounds by host cell enzymes . Because it requires the viral kinase for initial phosphorylation, acyclovir is selectively activated, and the active metabolite accumulates, only in infected cells. Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms: competition with deoxyGTP for the viral DNA polymerase, resulting in binding to the DNA template as an irreversible complex; and chain termination following incorporation into the viral DNA

DNA POLYMERASE INHIBITORS, DPIs

Indications

- Primary genital herpes
- Herpes labialis
- Management of zoster associated pain
- Given prophylactically to patients undergoing organ transplantation to prevent reactivation of HSV infections
- Treatment of herpes simplex encephalitis, neonatal HSV infections and serous HSV or VZV infections

Available dosage forms: oral: 200 mg capsules, 400, 800 mg tablets; 200 mg/5 ml suspension. Parenteral: 50 mg/ml powder to reconstitute injection (500, 1000 mg/vial), topical: 5% ointment

Dose

- **Oral**
- First episode genital herpes 400 mg tid or 200 mg five times daily
- Recurrent genital herpes 400 mg tid or 200 mg five times or 800 mg bid
- Genital herpes suppression 400 mg bid
- Herpes proctitis 400 mg five times daily
- Mucocutaneos herpes 400 mg five times daily

DPIs

- **Oral cont..**
- Varicella 20 mg/kg (maximum 800 mg) four times daily
- Zoster 800 mg five times daily

Intravenous

- Severe HSV infection 5 mg/kg q8h
- Herpes encephalitis 10-15 mg/kg q8h
- Neonatal HSV infection 20 mg/kg q8h
- Varicella zoster suppression in immunocompromised host 10mg/kg q8h
- **Interactions**
- Has no serious interactions

Adverse effects

- Acyclovir is generally well tolerated
- IV infusion may cause reversible renal dysfunction due to crystalline neuropathy or neurologic toxicity (tremors, delirium, seizures)

DPIs cont….

Mangement of ADR

- Adequate hydration

Half-life, metabolism and excretion

- Hal life is approximately 3 hours in patients with normal renal function and 20 hours in patients with anuria
- Acyclovir is cleared by glomerular filtration and tubular secretion
- Acyclovir is cleared by hemodialysis but not by peritoneal dialysis.

DPIs cont…

2. VALACYCLOVIR

- It's the L-valyl ester of acyclovir. It s rapidly converted to acyclovir after oral administration
- It has improved efficacy versus acyclovir for all indications

Indications

- Treatment of first attacks of recurrent genital herpes
- Suppression of recurrent genital herpes
- Treatment of herpes zoster infections
- Preventing cytomegalovirus disease after organ transplantation
- Available dosage forms: oral: 500, 1000 mg tablets

Dose

Oral

- First episode genital herpes 1g bid
- Recurrent genital herpes 500 mg bid
- Genital herpes suppression 500 mg daily or twice daily
- Zoster 1 g tid

DPIs cont…

Adverse effects

- Generally well tolerated
- Nausea, headache and diarrhea may occur
- High doses in AIDS patients may cause GIT intolerance as well as thrombotic microangiopathies such as thrombotic purpura and hemolytic uremic syndrome

3. **FAMCICLOVIR**

- It is the diacetyl ester prodrug of 6-deoxypenciclovir, an acyclic guanosine analogue
- Active against HSV-1, HSV-2,VZV, EBV, and HBV

Indications

- Treatment of first and recurrent genital herpes attacks and for chronic daily suppression
- Treatment of acute herpes zoster (shingles)
- Available dosage forms: oral: 125, 500 mg tablets

DPIs cont…

Dose:

- **Oral**
- First episode genital herpes 250 mg tid
- Recurrent genital herpes 125 mg bid
- Genital herpes suppression 250 mg bid
- Zoster 500 mg tid

Adverse effects

- Generally well tolerated
- Headache, diarrhea and nausea may occur

Half life metabolism and elimination

- After oral administration, famciclovir is rapidly converted by first pass metabolism to penciclovir, which shares many features with acyclovir
- Penciclovir has intracellular half life is 10 hours in HSV-1 infected cells, 20 hours in HSV-2 infected cells and 7 hours in VZV infected cells in vitro
- Penciclovir is excreted primarily in urine

DPIs cont..

4. GANCICLOVIR

Indications

- Delay progression of CMV retinitis in patients with AIDs
- Treatment of CMV colitis and esophagitis
- Reduce risk of CMV infections in transplant patients
- Treatment of CMV pneumonitis in immunocompromised patients
- Available dosage forms: oral: 250,500 mg capsules; parenteral: 500 mg/vial for IV injection; intraocular implant (vitrasert): 4.5 mg ganciclovir/implant

Dose

- Intravenous
- CMV retinitis treatment induction: 60mg/kg q8h or 90 mg/kg q12h, maintenance: 5 mg/kg/d or 6 mg/kg five times daily

DPIs cont…

Oral

- CMV prophylaxis 1 g tid
- CMV retinitis treatment (maintenance only) 1 g tid

Intraocular implant

- CMV retinitis treatment 4.5 mg every 6-8 months

Adverse effects and drug interactions

- most common adverse effect o, is myelosuppression. Myelosuppression may be additive in patients receiving concurrent zidovudine, azathioprine, or mycophenolate mofetil. Other potential adverse effects are nausea, diarrhea, fever, rash, headache, insomnia, and peripheral neuropathy, as well as retinal detachment in patients with CMV retinitis. Central nervous system toxicity (confusion, seizures, psychiatric disturbance) and hepatotoxicity have been rarely reported.
- Levels of ganciclovir may rise in patients concurrently taking probenecid or trimethoprim. Concurrent use of ganciclovir with didanosine may result in increased levels of didanosine

DPIs cont..

Management of ADRs

- Drug withdrawal in myelosuppression
- Pyridoxine 50 mg od for nueropathy

Half life, metabolism and excretion

- Half life is 2-4 hours with normal renal function
- Clearance of the drug is linearly related to creatinine clearance
- Ganciclovir is readily cleared by hemodialysis

5. VALGANCICLOVIR

Indications

- Treatment of CMV retinitis in patients with AIDs
- **Available dosage forms:** oral: 450 mg capsules

Dose

Oral

- CMV retinitis induction: 900 mg bid, maintenance : 900 mg od
- CMV prophylaxis 900 mg od

DPIs cont…

Pharmacokinetics

- Well absorbed and rapidly metabolized in the intestinal wall and the liver to ganciclovir
- Absolute bioavailability is 60%
- Major route of elimination is renal through glomerular filtration and tubular secretion

6. CIDOFOVIR

- It is a cytosine nucleoside analog with in vitro activity against CMV, HSV-1, HSV-2, VZV, EBV, HHV-6, HHV-8, adenovirus, poxviruses, polyomaviruses and human papillomavirus

Indications

- Treatment of CMV retinitis, given IV
- Treatment of polyomaviruses-associated progressive multifocal leukoencephalopathy syndrome in AIDS patients
- Post exposure prophylaxis against small pox
- Topical treatment of molluscam contagiosam
- **Available dosage form**: Parenteral: 375 mg/vial (75 mg/ml) for IV injection

Dose:

- **Intravenous**
- CMV retinitis induction: 5 mg/kg every 7 days, maintenance: 5 mg/kg every 14 days

DPIs cont…

Interactions

- Probenecid coadministration blocks active tubular secretion and decreases nephrotoxicity
- Intravenous cidofovir must be administered with probenecid (2 g at 3 hours prior to infusion and 1 g at 2 hours after)

Precautions

- Adjust dosage in case of alterarions of calculated creatinine clearance or the presence of urine protein prior to infusion

Contraindication

- Renal insufficiency
- Concurrent administration of potentially nephrotoxic agents e. g. amphotericin B, aminoglycosides, NSAIDs, pentamidine, foscarnet)

Adverse reactions

- Dose dependent nephrotoxicity
- Uveitis
- Decreased intraocular pressure
- Probenecid related hypersensitivity reactions
- Rare neutropenia and metabolic acidosis

DPIs cont….

Management of ADR

- Probenecid 2g at 3 hours prior to infusion and 1g at 2 and 8 hours after to decrease nephrotoxicity

Half life , metabolism and excretion

- Terminal hal life is about 2.6 hours and the active metabolite , cidofovir diphosphate has intracellular half life of 17-65 hours
- A separate metabolite, cidofovir phosphocholine, has a half life of atleast 87 hours and may serve as intracellular reservoir of active drug
- Elimination involves active tubular secretion

DPIs cont…

7. FOSCARNET

- Foscarnet (phosphonofomic acid) is an inorganic pyrophosphate compound that inhibits viral DNA polymerase, RNA polymerase and HIV reverse transcriptase directly , without requiring activation by phosphorylation
- It has invitro activity against HSV, VZV, CMV, EBV, HHV-6, HHV-8 and HIV

Indications

- CMV retinitis
- CMV colitis and esophagitis
- Acyclovir resistant HSV infections and VZV infections

Available dosage forms:Parenteral 24 mg/ml for IV injection

Dose

Intravenous:

- CMV retinitis treatment induction: 60 mg/kg q8h or 90 mg/kg q12h, maintenance: 90-120 mg/kg/d

DPIs CONT….

Adverse reactions

- Renal insufficiency
- Hypo or hypercalcemia
- Penile ulcerations
- Nausea, vomiting and fatique
- Anemia
- CNS toxicity include headache, hallucination and seizures
- Chromosomal damage

Management of ADRS

- Saline preloading helps to prevent nephrotoxicity and also avoid concomitant use with drugs that have nephrotoxic potential e.g amphotericin B, pentamidine and aminoglycoside
- Hypocalcemia: avoid pentamidine to reduce the risk; give calcium gluconate
- Anemia: avoid zidovudine, iron and folic acid, transfuse if severe

Contraindications

- Patients on zidovudine, pentamidine, amphotericin B and aminoglycosides
- Renal insufficiency

Interactions

- Concurrent use with pentamidine increases risk of severe hypocalcemia
- Concurrent use with amphotericin B and aminoglycosides increases risk of nephrotoxicity
- Zidovudine increases risk of severe anemia

DPIs cont…

Pharmacokinetics

- Mean plasma half life is 4.5- 6.8 hours; upto 30% of the drug may be deposited in bone, with a half life of several months
- Clearance is primarily by the kidney and is directly proportionate to creatinine clearance

8. **FOMIVIRSEN**

- It is an oligonucleotide that inhibits human CMV through antisense mechanism

Mechanism of action

- Binding of fomivirsen to target m RNA results in inhibition of immediate early region 2 protein synthesis, thus inhibiting virus replication

Indication

- Treatment of CMV retinitis in patients with AIDs especially those unresponsive to alternative therapies

Available dosage forms: intravitreal:(vitravene) 6.6 mg/ml for injection

Dose

- Intravitreal injection CMV retinitis treatment induction: 330 ug (microgram) every 14 days, maintenance: 330 ug every 4 weeks

Adverse effects

- Iritis and vitreitis
- Increased intraocular pressure
- Changes in vision

DPIs cont....

Precautions

- An interval of atleast 2-4 weeks is recommended between cidofovir administration and use of fomivirsen because of risk of ocular inflammation

Half life and excretion

- The drug is slowly cleared from vitreous with a half life of about 55 hours in humans
- Measurable concentrations of the drug is not detected in the systemic circulation following intravitreal administration

8. PENCICLOVIR

- The guanosine analog penciclovir, the active metabolite of famciclovir, is also available for topical use. One percent penciclovir cream is effective for the treatment of recurrent herpes labialis in immunocompetent adults . Side effects are uncommon

INHIBITORS OF VIRAL COAT DISASSEMBLY AND NEURAMINIDASE

- This class include: amantadine and rimantadine, zanamivir and oseltamivir

AMANTADINE AND RIMANTADINE

Mechanism of action

- Are cyclic amines that inhibit uncoating of viral RNA influenza A within infected host cells, thus preventing its replication

Indications

- Viral influenza A infections

Available dosage forms

- Amantadine: (symmetrel); oral: 100 mg capsules, tablets; 50 mg/5 ml syrup
- Rimanatdine: (flumadine): Oral: 100 mg tablets; 50 mg/ml suspension

Dose

- Amantadine 100 or 200 mg bd orally in influenza A
- Rimantadine 100 or 200 mg bd orally in influenza A

ANTI-INFLUENZA DRUGS

Adverse effects

- GIT intolerance
- CNS complaints(nervousness, difficulty in concentrating and light headedness)

Contraindications

- Pregnancy; may cause birth defects

Interactions

- Concomittant use of amantadine with antihistamines, anticholinergic drugs, hydrochlorothiazide, trimethoprim-sulfamethoxazole increases CNS toxicity

Precautions

- High plasma concentrations of amantadine (1-5 ug/ml) results into serious neurotoxic reactions
- Dose reductions for both agents in renal insufficiency and for amantadine in hepatic insufficiency

ANTI-INFLUENZA DRUGS

Half life, metabolism and excretion

- Plasma hal life is 12-18 hours for amantadine and 24-36 hours for rimantadine
- Rimantadine is four to ten times more active than amantadine in vitro
- Amantadine is excreted unmetabolized in urine, rimantadine undergoes extensive hydroxylation, conjugation and glucuronidation before renal/urinary excretion

ANTI-INFLUENZA DRUGS

ZANAMIVIR AND OSELTAMIVIR

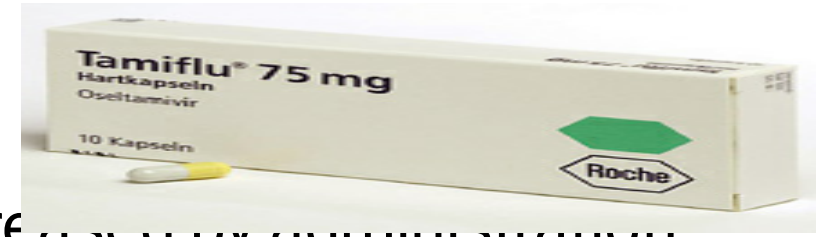
- Are neuraminidase inhibitors
- Have activity against both influenza A and B

Indication

- Treatment of acute uncomplicated influenza infections

Available dosage forms:

- Zanamivir (Relenza):inhalational: 5 mg
- Oseltamivir (Tamiflu): oral: 75 mg capsule; powder to reconstitute as suspension (12 mg/ml)



Dose:P.O 75 mg bd

Adverse effects

- Nausea and vomiting which may be decreased by administration with food

Halflife metabolism and excretion

- Zanamavir is administered via oral inhalation; it has poor oral bioavailablity, rapid renal clearance and abscence metabolism
- Oseltamivir is a prodrug that is activated in the gut or liver; its half life is 6-10 hours and excretion is primarily in urine

ANTI-HEPATITIS AGENTS

- This class include: ribavirin, lamivudine, adefovir, interferon alfa, pregylated interferon alpha

1. **RIBAVIRIN**

- A guanosine analogue that is phosphorylated intracellularly by host cell enzyme

Mechanism of action

- Interferes with synthesis of guanosine triphosphate, to inhibit capping of viral messenger RNA and to inhibit viral RNA – dependent RNA polymerase of certain viruses

Indication

- Treatment of chronic hepatitis C in combination with SC interferon alfa-2b; monotherapy is not effective.
- Viral hemorrhagic fever

Interactions

- Antacids reduces bioavailability
- High fat meals increases bioavailability

Adverse effects

- Dose dependent hemolytic anemia
- Depression ,fatigue, irritability, rash , insomnia, cough,pruritus

ANTI-HEPATITIS AGENTS

Management of ADRs

- Dose reduction to prevent hemolytic anemia

Available dosage forms:

- Aerosol (virazole): powder to reconstitute for aerosol; 6g/100 ml vial. Oral (rebetol) 200 mg capsule; oral: (rebetron): 200 mg in combination with 3 million units of interferon

Contraindications

- anemia
- End stage renal failure
- Severe heart disease
- Pregnancy

Pharmacokinetics

- Bioavailability is about 60%
- Eliminated in urine

ANTI-HEPATITIS AGENTS

2. ADEFOVIR

- A nucleotide analog of adenosine monophosphate

Indication

- Treatment of lamivudine resistant strains of hepatitis B
- **Available dosage form:** oral: 10 mg tablets
- **Dose**: chronic HBV 10 mg od orally

Adverse effects

- Dose dependent nephrotoxicity
- Lactic acidosis
- Hepatomegally with steatosis

Interactions

- Ibuprofen increases bioavailability of adefovir by 23%

Pharmacokinetics

- Terminal elimination half life is about 7.5 hours
- Excreted in the kidneys by glomerular filtration and tubular reabsorption

DRUGS THAT MODULATE HOST IMMUNE SYSTEM

1. INTEFERONS

- Interferons are host cytokines that exert complex antiviral, immunomodulatory, and antiproliferative activities. Interferon (IFN)-alfa appears to function by induction of intracellular signals following binding to specific cell membrane receptors, resulting in inhibition of viral penetration, translation, transcription, protein processing, maturation, and release, as well as increased expression of major histocompatibility complex antigens, enhanced phagocytic activity of macrophages, and augmentation of the proliferation and survival of cytotoxic T cells

Indications

- Treatment of hepatitis B (dose: SC/IM 5 million units od)
- Hepatitis C; Dose: SC/IM 5 million units od for 3 weeks, then 5 million units three times weekly.

IMMUNOMODULATORS

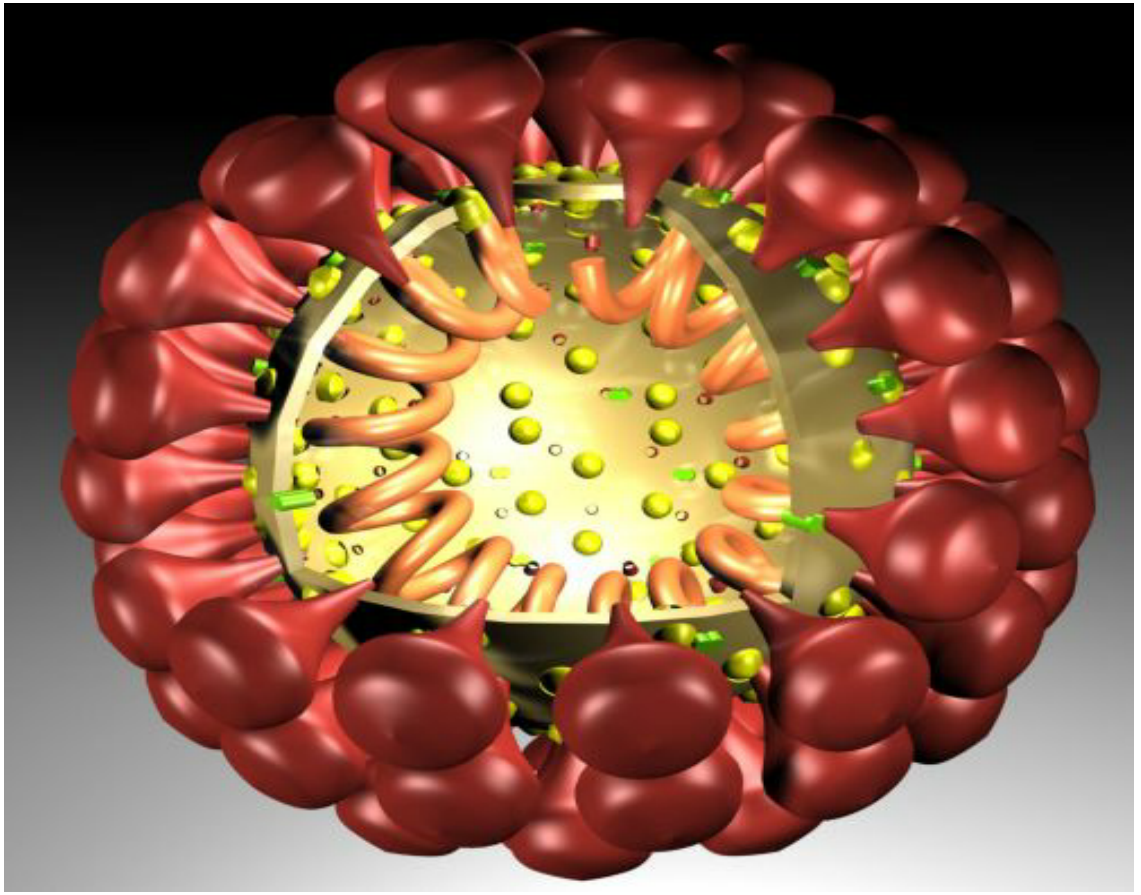
2. PALIVIZUMAB

- Palivizumab is a humanized monoclonal antibody directed against an epitope in the A antigen site on the F surface protein of RSV (respiratory syncytial virus). It is licensed for the prevention of RSV infection in high-risk infants and children such as premature infants and those with bronchopulmonary dysplasia or congenital heart disease. Potential **adverse effects include:** upper respiratory tract infection, fever, rhinitis, rash, diarrhea, vomiting, cough, otitis media, and elevation in serum aminotransferase levels.

3. IMIQUIMOD

- Imiquimod is an immune response modifier shown to be effective in the topical treatment of external genital and perianal warts (ie, condyloma acuminatum). The 5% cream is applied three times weekly and washed off 6–10 hours after each application. Imiquimod is also effective against actinic keratoses. Local skin reactions are the most common side effect; these resolve within weeks after therapy. However, pigmentary skin changes may persist. Systemic adverse effects such as fatigue and influenza-like syndrome have occasionally been reported.

THE END…



- THANK YOU.