Non retroviral – Anti-viral drugs

Non–retro viruses controlled by current antiviral therapy

- Herpes viruses
- Cytomegalovirus (CMV)
- Hepatitis viruses
- Influenza viruses (the “flu”)
- Respiratory syncytial virus (RSV)

Antiviral drugs- classification

- A)Anti herpes (DNA virus) drugs- acyclovir, valacyclovir, famciclovir, ganciclovir, valganciclovir, idoxuridine, trifluridine, cidofovir, foscarnet
- B)Anti influenza (RNA)virus drugs- amantadine, rimantadine, oseltamivir, zanamivir, peramivir
- C) Anti-cytomegalovirus
- D)Anti-hepatitis (BOTH)virus drugs

  HBV- lamivudine, entecavir, adefovir dipivoxil, tenofovir, telbivudine

  HCV- ribavirin etc.

ANTI-HERPES VIRUS DRUGS

- EFFECTIVE AGAINST HERPES GROUP OF DNA VIRUSES
- *HERPES SIMPLEX VIRUS – 1 (HSV-1), HERPES SIMPLEX VIRUS – 2 (HSV-2), VARICELLAZOSTER VIRUS (VZV), EPSTEIN-BARR VIRUS (EBV) AND CYTOMEGALOVIRUS (CMV)*

Antiherpes/Varicella zooster Agents

- **Acyclovir-** *prototype*
- **Valacyclovir**
- **Famciclovir**
- **Penciclovir**
- **Trifluridine**
- **Vidarabine**
- **idoxuridine**
- **foscarnet**

Pharmacology of acyclovir and congeners

- All are guanosine nucleoside analogues.
- Valacyclovir is prodrug of acyclovir
- Famciclovir is prodrug of penciclovir.
- Penciclovir is used only topically whereas Famciclovir can be administered orally.

Acyclovir

- an acyclic guanosine derivative
- Phosphorylated by *viral thymidine kinase*
- Di-and tri-phosphorylated by host cellular enzymes
- Inhibits viral DNA synthesis by:
  - 1) competing with dGTP for viral DNA polymerase
  - 2) chain termination

Pharmacokinetics of Acyclovir :

- Oral bioavailability ~ 20-30%
- Distribution in all body tissues including CNS
- Renal excretion: > 80%
- Half life: 2-5 hours
- Administration: Topical, Oral , IV depending on severity and recurrences.

Mechanism of Action of Acyclovir

- Acyclovir is phosphorylated by a viral thymidine-kinase, then metabolized by host cell kinases to nucleotide analogues.
- The analogue inhibits viral DNA-polymerase.
- Acyclovir is thus selectively activated in cells infected with herpes virus.
- Uninfected cells do not phosphorylate acyclovir

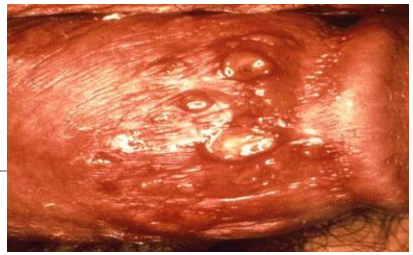
Mechanism of Resistance

Acyclovir

- Alteration in viral thymidine kinase
- Alteration in viral DNA polymerase
- Cross-resistance with *valacyclovir, famciclovir,* and *ganciclovir*

Anti-viral spectrum

- Acyclovir: HSV-1, HSV-2, VZV, Shingles.
- Ganciclovir / Cidofovir : CMV
- Famciclovir : Herpes genitalis and shingles
- Foscarnet : HSV, VZV, CMV, HIV
- Penciclovir : Herpes labialis
- Trifluridine : Herpetic keratoconjunctivitis



1. GENITAL HERPES SIMPLEX: HSV – II (TOPICAL, ORAL AND IV))
   - PRIMARY DISEASE: GENERALLY OINTMENT IN MILD – MORE SEVERE CASES –ORAL (1 GM/DAY IN 5 DIVIDED DOSES)
   - –RECURRENT DISEASE: ORAL (NOT EFFECTIVE) – IV (5 MG/KG INFUSED OVER 1 HOUR Q 8 HRLY FOR 10 DAYS)
   - (SUPPRESSIVE ORAL THERAPY 400 MG BD – PREVENT RECURRENCES – CONTINUOUS ORAL THERAPY FOR CASES WITH >8 RECURRENCES PER YEAR)

1. MUCOCUTANEOUS *H. SIMPLEX*: HSV –I
   - ACYCLOVIR CREAM
   - ORAL OR IV IN IMMUNOCOMPROMIZED PATIENTS (15 MG/KG/DAY FOR 7 DAYS)

1. *H. SIMPLEX* ENCEPHALITIS: DOC TYPE – 1
   - 10 TO 20 MG/KG/8HR X 10 DAYS

1. *H. SIMPLEX* KERATITIS: SUPERFICIAL DENDRITIC CORNEAL ULCER BETTER THAN IDOXURIDINE (BETTER PENETRATION) – PREVENTION OF BLINDNESS

2. *H. ZOSTER* – LESS SUSCEPTIBLE – USED ONLY IN IMMUNODEFICIENT PATIENTS – ALSO ORAL AND OINTMENT THERAPY

3. *CHICKENPOX:* WITH IMMUNODEFICIENCY – DOC –15 MG/KG/DAY IV FOR 7 DAYS – ALSO PROPHYLACTIC VALUE

Clinical Uses

- Oral, IV, and Topical formulations
- Cleared by glomerular filtration and tubular secretion
- ***Uses:***
  - Herpes Simplex Virus 1 and 2 (HSV)
  - Varicella-zoster virus (VZV)
- ***Side Effects:*** nausea, diarrhea, headache, tremors, and delirium

Adverse effects of Acyclovir

- Nausea, vomiting and diarrhea
- Nephrotoxicity- crystalluria, haematuria, renal insufficiency
- Myelosuppression- Neutropenia and thrombocytopenia- Ganciclovir

Valacyclovir

- L-valyl ester of acyclovir
- Converted to acyclovir when ingested
- ***M.O.A.:*** same as acyclovir
- ***Uses:***
  - 1) recurrent genital herpes
  - 2) herpes zoster infections
- ***Side Effects:*** nausea, diarrhea, and headache

Famciclovir

- Prodrug of ***penciclovir*** (a guanosine analog)
- ***M.O.A.:*** same as acyclovir
- does **not** cause chain termination
- ***Uses:*** HSV-1, HSV-2, VZV, EBV, and hepatitis B
- ***Side Effects****:* nausea, diarrhea, and headache

Summary

Acyclovir is the drug of choice for

- HSV Genital, mucocutaneous infections
- HSV encephalitis, keratitis
- Herpes zoster, chicken pox
- HSV infections in immunocompromised persons.

Ganciclovir is the drug of choice for:

- CMV retinitis in immunocompromised patient
- Prevention of CMV disease in transplant patients

Trifluridine

- Trifluridine- fluorinated pyrimidine
  - inhibits viral DNA synthesis same as acyclovir
  - incorporates into viral and cellular DNA
  - ***Uses***: HSV-1 and HSV-2 (topically)

Vidarabine

- An adenosine analog
- inhibits viral DNA polymerase
- incorporated into viral and cellular DNA
- metabolized to hypoxanthine arabinoside
- ***Side Effects***: GI intolerance and myelosuppression

Foscarnet

- an inorganic pyrophosphate analogue unrelated to any nucleic acid precursor.
- It directly inhibits viral DNA and RNA-polymerase and viral inverse transcriptase(it does not require phosphorylation for antiviral activity)
- HSV-1, HSV-2, VZV, CMV and HIV.
- Oral bioavailability ~ 10-20% so given I.V.

  Distributed to all tissues including CNS
- Adverse effects- Hypocalcemia and hypomagnesemia (due to chelation of the drug with divalent cations) are common, neurotoxic,nephrotoxic, renal diabetes, anaemia.

Contd..

Therapeutic uses of Foscarnet

- It is an alternative drug for

  -HSV infections (acyclovir resistant / immunocompromised patient)

  -CMV retinitis (ganciclovir resistant / immunocompromised patient

Anti-Cytomegalovirus Agents

Anti-Cytomegalovirus Agents

- **Gancyclovir**
- **Valgancyclovir**
- **Cidofovir**
- **Foscarnet**
- **Fomivirsen**

Ganciclovir

- An acyclic guanosine analog
- requires triphosphorylation for activation
- monophosphorylation is catalyzed by a phosphotransferase in CMV and by thymidine kinase in HSV cells
- ***M.O.A.:*** same as acyclovir
- ***Uses***: CMV*, HSV, VZV,and EBV
- ***Side Effect***: myelosuppression

Valgancyclovir

- Monovalyl ester prodrug of gancyclovir
- Metabolized by intestinal and hepatic esterases when administered orally

- ***M.O.A.:*** same as gancyclovir
- ***Uses***: CMV*
- ***Side Effect***: myelosuppression

Cidofovir

It is approved for the treatment of CMV retinitis in immunocompromised patients (ganciclovir failure)

- It is a nucleotide analogue of cytosine– no phosphorylation required.
- It inhibits viral DNA synthesis
- Available for IV, Intravitreal inj, topical on anogenital warts.
- weekly given.
- Nephrotoxicity is a major disadvantage.
- Given with pre and post dose oral probeneacid which inhibits its tubular secretion increasing availability and decreases nephrotoxicity.

Cidofovir

- Aphosphorylation cytosine analog
- **not** dependent on viral enzymes
- ***Uses:*** CMV*, HSV-1, HSV-2, VZV, EBV, HHV-6, adenovirus, and human papillomavirus
- ***Side Effects:*** nephrotoxicity (prevented by admin. of probenecid)
- ***Resistance:*** mutation in DNA polymerase gene

Foscarnet

- An inorganic pyrophosphate
- inhibits viral DNA polymerase, RNA polymerase, and HIV reverse transcriptase
- does not have to be phosphorylated
- ***Uses:*** HSV, VZV, CMV, EBV, HHV-6, HBV, and HIV
- Resistance due to mutations in DNA polymerase gene
- ***Side Effects:*** hypo- or hypercalcemia and phosphotemia

Fomivirsen

- An oligonucleotide
- ***M.O.A.:*** binds to mRNA and inhibits protein synthesis and viral replication
- ***Uses***: CMV retinitis
- ***Side effects***: iritis and increased intraocular pressure

Table 49–2. Agents to treat cytomegalovirus (CMV) infection.

Agent	Route of Administration	Use	Recommended Adult Dosage
[redacted][1]	Intravenous	CMV retinitis treatment (induction or maintenance)	Induction: 5 mg/kg every 7 days Maintenance: 5 mg/kg every 14 days
[redacted]	Intravitreal injection	CMV retinitis treatment (induction or maintenance)	Induction: 330 µg every14 days Maintenance: 330 µg every 4 weeks
[redacted][1]	Intravenous	CMV retinitis treatment (induction or maintenance)	Induction: 60 mg/kg q8h or 90 mg/kg q12h Maintenance: 90–120 mg/kg/d
[redacted][1]	Intravenous	CMV retinitis treatment (induction or maintenance)	Induction: 5 mg/kg q12h Maintenance: 5 mg/kg/d or 6 mg/kg five times per week
	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
[redacted][1]	Oral	CMV retinitis treatment (induction or maintenance)	Induction: 900 mg bid Maintenance: 900 mg qd The drug should be taken with food.
	Oral	CMV prophylaxis	900 mg qd

[1]Dosage must be reduced in patients with renal insufficiency.

Anti-influenza agents

- Infuenza virus is a RNA virus which causes respiratory infections
- Segmented genome and core proteins define its type A, B, C.
- A- produces pandemics, epidemics and B- produces sporadic infections
- H5N1 (bird flu) and H1N1 (swine flu) are prevalent now.

Anti-influenza drugs

- Amantadine / Rimantadine (prevent uncoating by inhibiting M2 proteins)
- Oseltamivir / Zanamavir/Peramivir(viral neuraminidase inhibitors)

RSV bronchiolitis– Ribavirin

Anti-influenza agents

~~Amantadine, Rimantadine~~

- Inhibits influenza virus A
  - Resistance wide spread
  - Used for both prophylaxis and treatment
- Acts on M2 ion channel
  - Early step (uncoating) as well as late step (viral assembly)
- Resistance: mutation of M2 protein

Amantadine and Rimantadine (methyl derivative)

-Tricyclic amine unrelated to any nucleic acid precursor

- Prevention & Treatment of influenza A (not B)
- Inhibition of viral uncoating by inhibiting the viral membrane protein M2
- Oral bioavailability ~ 50-90%
- Amantadine cross extensively BBB whereas Rimantadine does not cross extensively
- Dose P-100mgOD; T/t 100mg BD for 5 days
- Not preferred now
- Amantadine has anti-parkinsonian effects also.

- Pharmacokinetics:
  - Well absorbed orally
    - Rimantadine- higher bioavailability
  - Excreted unchanged in urine over 2-3 days
    - Rimantadine metabolised and eliminated slowly ($t_{½}$ 30 hrs)

- Adverse effects:
  - Generally well tolerated
  - Nausea, anorexia, insomnia, dizziness, nightmares, lack of mental concentration, hallucinations
  - Ankle edema
- Rimantadine: better tolerated

PHARMACOLOGY OF AMANTADINE AND CONGENERS

Chemistry

-**Amantadine** and rimantadine are tricyclic amines.

Mechanism of action

-***Inhibition of viral uncoating*** by:

a) Blockade of the viral membrane matrix protein M2, which function as an ion channel. This channel is required for the fusion of the viral membrane with the cell membrane.

b) Rising the pH of the endosome (an acidic pH inside the endosome is required for viral uncoating)

Antiviral spectrum and resistance

-Influenza A virus (not B and C virus)

-Resistant variants are selected rapidly during treatment (approximately in 30% of treated patients)

Other effects

-Amantadine has antiparkinsonian effects. The mechanism of action is not clear but it may be related to:

a) the antimuscarinic properties of the drug

b) the stimulation of the synthesis and release of dopamine (and other catecholamines)

Pharmacokinetics and administration (amantadine)

-F(oral): 50-90%

-Distribution in all body tissues including CNS

-Renal excretion: > 90%

-Half lives: » 16 hours

-Administration: oral

Adverse effects

-Anorexia, nausea and vomiting ,stypsis, xerostomia, urinary retention.

-Nervousness ,insomnia, lightheadedness, difficulty concentrating, ataxia

-Delirium, hallucinations, seizures (with high doses)

-Teratogenic effects in animals

Therapeutic uses

-Treatment of influenza A (treatment within the first 48 hours after the exposure reduces the duration of symptoms and speeds functional recovery)

-Prevention of influenza A (70-90% protective). The drugs do not impair the immune response to influenza A vaccine.

Neuraminidase inhibitors :

- Prevent the release of new virions and their spread from cell to cell.
- Broad spectrum so against type A and B both.
- Oseltamivir requires activation to oselamivir carboxylate by liver esterases so may not be effective in infants.
- More useful if given in initial 48 hrs.

Contd..

- Do not interfere with immune response to influenza A vaccine.
- Can be used for both prophylaxis and acute treatment.
- A/E- nausea, weakness, abdominal pain, diarrhoea, cough, skin reactions

Anti-influenza agents: Oseltamivir

- Prodrug
- Active against Influenza A, Influenza B
- Acts by inhibiting virus neuraminidase enzyme
  - Required for release of viruses (last step)
- Resistance: mutation of neuraminidase

Anti-influenza agents: Oseltamivir

- Use:
  - Prophylaxis: Influenza A, swine flu, bird flu, influenza B
  - Treatment: Influenza A, swine flu, bird flu, influenza B
- Oseltamivir resistant strains may be sensitive to zanamivir or vice versa
- Side effects:
  - Gastric irritation, skin reaction

Anti-influenza agents: Zanamivir

- Similar to oseltamivir
- Poor oral absorption
  - Administered by inhalation
- To be used as alternative to oseltamivir
- Side effects:
  - Bronchospasm (CONTRAINDICATED IN ASTHMA PATIENTS)
  - Headache, dizziness, nausea, rashes

Contd...

- Zanamavir is given intranasally, useful in oseltamivir resistant cases also.
- Risk of bronchospasm with zanamavir.
- Laninamivir- long acting inhaled neuraminidase inhibitor against oseltamivir resistant virus.
- Peramivir- drug given i.v., single dose 600 mg treatment.

ANTI-HEPATITIS VIRUS DRUGS

Hepatic viral infections

Hepatic Viral infections:

AIM : HBV- suppression of replication

HCV- eradication

HBV is DNA virus which integrates into host Dna like HIV virus and can cause permanent, latent infection.

HCV is RNA virus which do not integrate so can be eradicated.

- Interferons and ribavirin are non specific antiviral agents.

- SOME ANTIVIRAL DRUGS ARE VIRUS-NONSELECTIVE – INHIBIT VIRUSES BELONGING TO DIFFERENT CLASSES (DNA – RNA)
- FOR HEPATITIS B: LAMIVUDINE, ADEFOVIR DIPIVOXIL, TENOFOVIR
- FOR HEPATITIS C: RIBAVIRIN, INTERFERON A

- HEPATITIS B (HBV) IS A DNA VIRUS – INTEGRATE INTO HOST CHROMOSOME AND PERMANENT INFECTION
- HEPATITIS C (HCV) IS RNA VIRUS – DOES NOT INTEGRATE INTO HOST CHROMOSOME CAUSE CHRONIC HEPATITIS

Anti-Hepatitis Agents

- **Lamivudine (3TC)** -Nucleoside Reverse Transcriptase Inhibitor (NRTI)
- **Adefovir** -Nucleotide Inhibitor
- **Interferon Alfa**
- **Pegylated Interferon Alfa**
- **Ribavirin**

Interferons

- are natural proteins produced by the cells of the host immune systems in response to challenges by foreign agents such as viruses, bacteria, parasites and tumor cells.

- Antiviral, immune modulating and anti-proliferative actions
- Three classes of interferons – α, β, γ

Contd..

- α and β interferons are produced by all the cells in response to viral infections
- γ interferons are produced only by T lymphocyte and NK cells in response to cytokines– immune regulating effects
- γ has less anti-viral activity compared to α and β interferons

Interferons

- ***Interferon Alfa***

- Endogenous proteins

- induce host cell enzymes that inhibit viral RNA translation and cause degradation of viral mRNA and tRNA
- Bind to membrane receptors on cell surface
- May also inhibit viral penetration, uncoating, mRNA synthesis, and translation, and virion assembly and release

Interferons

- ***Pegylated interferon Alfa***
- A linear or branced polyethylene gylcol (PEG) moiety is attached to covalently to interferon
- Increased half-life and steady drug concentrations
- Less frequent dosing
- Tx chronic hepatitis C in combination with ribavirin

Mechanism of action of Interferons

-act by JAK–STAT pathway to increase antiviral proteins, and promote formation of natural killer cells.

-Act at multiple steps like viral penetration, synthesis of viral RNA/ DNA, viral assembly and release. Used in chronic HBV and with ribavirin in acute HCV.

- Induction of:?????

1) a protein kinase which inhibits protein synthesis
2) an oligo-adenylate synthase which leads to degradation of viral mRNA
3) a phosphodiesterase which inhibit t-RNA

The action of these enzymes leads to an inhibition of translation

- Antiviral spectrum :

  Interferon α
- Includes HBV, HCV and HPV.
- Anti-proliferative actions may inhibit the growth of certain cancers - like Kaposi sarcoma and hairy cell leukemia.

Pharmacokinetics :

Interferons

- Oral bioavailability: < 1%
- Administered Intralesionally, S.C, and I.V
- Distribution in all body tissues, except CNS and eye.
- Half lives: 1-4 hours

Therapeutic uses of Interferons

- Chronic hepatitis B and C (complete disappearance is seen in 30%).
- HZV infection in cancer patients (to prevent the dissemination of the infection)
- CMV infections in renal transplant patients
- Condylomata acuminata (given by intralesional injection). Complete clearance is seen ~ 50%.
- Hairy cell leukemia (in combination with zidovudine)
- AIDS related Kaposi's sarcoma

Interferon α

- Other Therapeutic Uses:
  - Chronic hepatitis B/C
  - Condyloma acuminata
  - HSV, VZV, CMV
  - Chronic myeloid leukaemia, Follicular lymphoma, cutaneous T-cell lymphoma, multiple myeloma

Adverse effects of Interferons

- Acute flu-like syndrome (fever, headache)
- Bone marrow suppression (granulocytopenia, thrombocytopenia)
- Neurotoxicity (confusion, seizures)
- Cardiotoxicity– arrhythmia, hypotension
- Impairment of fertility
- Thyroid dysfunction, alopecia, hepatic dysfunction.

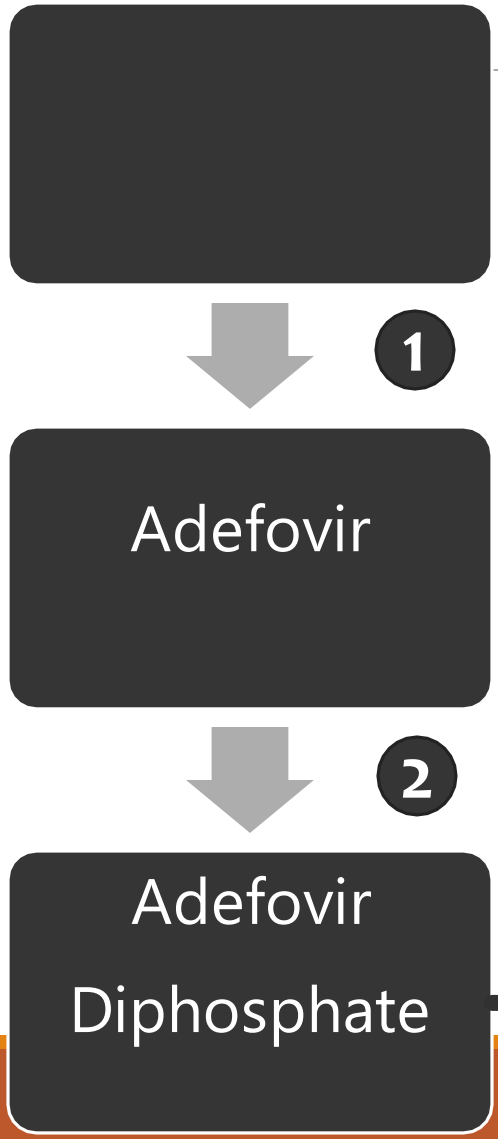
Specific Anti-hepatitis drugs for HBV

- DOC for treating chronic HBV is Entecavir
- Entecavir- guanosine analogue-viral DNA polymerase inhibitor, for lamivudine resistant HBV strains and chronic HBV.
- PK- taken empty stomach T1/2- 128-148 hrs.
- for lamivudine resistant HBV
- Tenofovir- another first line drug for chronic hepatitis, few GIT related adverse effects, 300mg OD, given as disoproxil prodrug

Anti-hepatitis agents: Adefovir

- Prodrug, Monophosphate analogue of AMP
- Active against HBV, other DNA and RNA viruses
- Use:
  - Chronic hepatitis B
  - Lamivudine resistant HBV
  - HBV with HIV infection

Anti-hepatitis agents: Adefovir



1. Esterases (intestine, liver)
2. Cellular kinases (within cells)

- Inhibits HBV DNA polymerase

- Gets incorporated into viral DNA
- Early termination of viral DNA

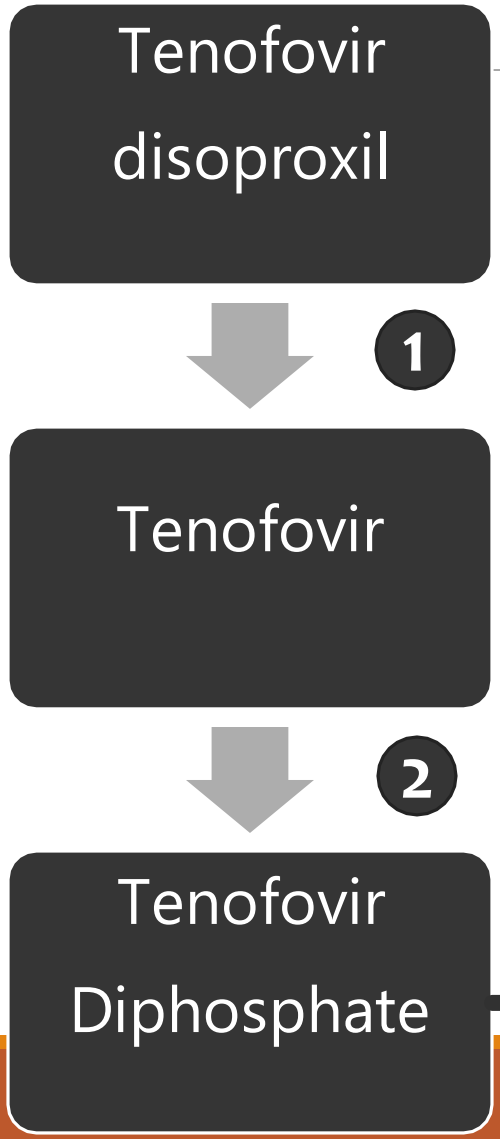
Anti-hepatitis agents: Adefovir

- Side effects:
  - Well tolerated at dose 10mg/day
  - Sore throat, headache, weakness, abdominal pain, flu syndrome
  - Nephrotoxicity
    - Higher dose
    - Predisposed
  - Lactic acidosis
    - With concurrent HAART therapy

Anti-hepatitis agents: Tenofovir (TDF)

- Monophosphate nucleotide related to AMP
- Active against HBV, HIV
- Use:
  - Chronic hepatitis B
  - Lamivudine resistance hepatitis B
- Well tolerated
  - Increase in Sr. Creatinine, Renal toxicity rare

Anti-hepatitis agents: Tenofovir



1. Esterases (intestine, liver)
2. Cellular kinases (within cells)

- Inhibits HBV DNA polymerase
- Inhibits HIV reverse transcriptase

- Gets incorporated into viral DNA
- Early termination of viral DNA

Ribavirin

- A guanosine analog
- phosphorylated intracellularly by host enzymes
- inhibits capping of viral messenger RNA
- inhibits the viral RNA-dependent RNA polymerase
- inhibits replication of DNA and RNA viruses

Ribavirin

- Use:
  - Hepatitis
    - Chronic hepatitis C: in combination with peginterferon
  - Severe influenza A/B
  - Measles
  - Herpes infection
  - Respiratory syncytial virus infection

Ribavirin

- Side effects:
  - Anaemia
  - Bone marrow depression
  - Haemolysis
  - Teratogenic
  - Can induce bronchospasm if used by inhalation

Questions???

- Thank you!