ANTIVIRAL AGENTS

HIV LIFE CYCLE

Stages of HIV life cycle

1.Bindind,fusion and entry

2.Transcription

3.Integration and replication

4.budding

5.Maturation

BINDING

For successful entry into the cells the HIV envelop glycoprotein 120 binds to the host receptor CD4 molecules

Coreceptors are necessary[CCR5 and CXCR4]

FUSION &ENTRY

Viral bindingto host cel ltriggers fusion of the viral and host cell membranes

Allows entry of virus core into host cell cytoplasm

Core protein dissolved by host enzyme releasing viral RNA and enzymes

INTEGRATION

RTenzymes converts the viral RNA into a DNA molecule .

The DNA enters the host cell nucleus

Integrase enzymes catalyses the process of integration of the viral DNA into the host cell’s DNA

REPLICATION

Integrated viral DNA turns the host cell into a factory for manufacturing more virus.

Viral proteins are produced as a single-protein molecule.

Viral proteins are cleared by protease enzyme .

BUDDING &MATURATION

Viral proteins together with RNA gather at the membrane of CD4 cells.

Viral particles are formed which bud off the cell and enter the blood stream.

The CD4 cell are often destroyed by HIV virus infection and replication resulting in profound immunodeficiency.

NRTIs[NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

1.ZIDOVUDINE

It’s a thymidine analogue[azidothymidine] the first and prototype NRTI

MIOA

Inhibits viral reverse transcriptase in preference to cellular DNA polymerase

PHARMACOKINETICS

Has rapid oral absorption

Bio availability is 65%

Has a plasma half life of 1hr because its rapidly cleared by hepatic glucuronidation

15-20% of the unchanged drug drug along with it’s noticeable life it’s excreted in urine

Crosses placenta and it’s found in milk

ADR

Most important

* Anaemia- aptatic anaemia
* Neutropenia

Others; - Nausea, Anorexia, Abnormal pain, headache, insomnia and myalgia

* - Myopathy, pragmentation of nails lactic acidosis , hepatomegaly
* INTERACTION
* PCM increases AZI toxicity probably by competing for Gluuronidation
* Azole antifungal inhibit AZI metabolism
* Together **with** other nephrotoxic and myelosuppressive drugs and probonecid enhances toxicity

*USES*

Used in combination of atleast 2 ARVS

2DIDANOSINE [DDL]

It’s a purine nucleoside analogue which after intracellular conversion to didanosine triphosphate competes with ATP for in corporation to viral DNA.

ADR

-Causes peripheral neuropathy

-Rarely pancreatitis

-Diarrhoea

-Abdominal pain

-Nausea & Dry mouth

DOSAGE

250Mg/day for less than or equal to 50 kg

400Mg/day for more than or equal to 60 kg B.W

2. STAVUDINE[d4T]

-Also thymidine analogue which acts same as zidovudine

ADR

-Peripheral neuropathy

-Lipodystrophy

-Lactic acidosis

DOSAGE

30Mg BD

LAMIVUDINE[3TC]

-It’s a deoxycytidine analogue which is phosphorylated intracellularly and inhibits HIV reverse transcriptase as well as HBV DNA polymerase

Pharmacokinetics

Has a high oral bioavailability as well as longer plasma t1/2 [6-8hrs]

Intracellular t1/2 is still longer than 12hrs

Mainly excreted unchanged in urine & can be employed in pts with hepatic insufficiency

Side effects

-Headache,Anorexia,Fatique,Abdominal pain ,Rashes ,Nausea, Pancreatitis,

-Neuropathy is rare

-Haematological toxicity does not occur

ABACAVIR [ABC]

It’s guanosine analogue which is clinically potent ARV drug that acts after intracellular conversion to it’s triphosphate

MOA

Carbovir triphosphate in intracellular gets incorporated in proviral DNA &terminates chain elongation

Pharmacok

-Has oral bioavailability of 80% and it’s mainly eliminated by metabolism

-Plasma t1/2 is 1-1.5hrs

-Intracellular t1/2 >12hrs

ADR

Hypersensitive rxns-;

\*Rashes, Abdominal pain ,Fever ,Bowel upset ,Flu-like respiratory syndrome

-Lypodystrophy

NOTE;

-Should be stopped when rxn occurs as fatalities have been recorded when pts developing these rxn were further given doses of ABC

DOSAGE

300Mg BD Or 600Mg OD

TENOFOVIR [TDF]

-It’s the only nucleotide analogue that’s commonly used as anti-HIV

Uses

-Anti-HIV

-Active against HBV

ADR

-Renal toxicity

-Osteoporosis

EMTRICITABINE [ FTC]

It’s fluorinated cytidine analogue which is converted intracellularly by cellular kinases into it’s triphosphate which acts as HIV reverse transcriptase inhibitor

Pharmacokinetics

-Absorbed orally ,little metabolized and largely excreted unchanged by the kidney

-Plasma t1/2 10 hrs ,intracellular t1/2 is longer more than 40 hrs permiting once daily

-Dose reduction in renal impairment

-shldn’t be used in coinfected pts[HIV-HBV pts] because it causes rise in viral load

Uses

-Used in HBV mgt

-Used as anti-HIV

ADR

-Fatigue

-Headache

-Nausea

-Diarrhoea

-Skin discoloration

DOSAGE

200Mg OD as FTC tablet.