Antiviral Agents

- Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cells.
- Antiviral agents must either block viral entry into or exit from the cell or be active inside the host cell.
- Antiviral agents are most active ,when viruses are replicating.
- The earlier that treatment is given , better the result.

Difficulties in treatment

1. Substantial multiplication has already occurred, before symptoms occur.
2. Intracellular – use host metabolic processes

   - Highly selective toxicity is harder to achieve.
3. Resistance to the drug

DNA VIRUSES

- **Adenoviruses** (URT & eye infection)
- **Hepadnaviruses** (hepatitis - B)
- **Herpesviruses** -
- Herpes Simplex Virus type -1 – causes oral herpes, ocular herpes , viral encephalitis ,herpes keratitis
- Herpes Simplex Virus type-2 – genital herpes
- Varicella Zoster Virus ˍ chicken pox, zoster or shingles
- Cytomegalovirus - infectious mononucleosis
- Epstein Barr virus – inf. mono, B-cell lymphoma
- **Papillomavirus** – warts
- **Poxvirus** – small pox

RNA VIRUSES

- **Picornaviruses** – Poliovirus causing polio & hepatovirus causing hepatitis-A
- **Orthomyxovirus –**influenza A,B,C – influenza,H1B1 causes swine flu
- **Paramyxoviruses** –rubella virus causing mumps , RSV causing LRTI,
- **Rhabdoviruses** – causing rabies
- **Arbovirus ,rotavirus,retrovirus,arenavirus, coronavirus**

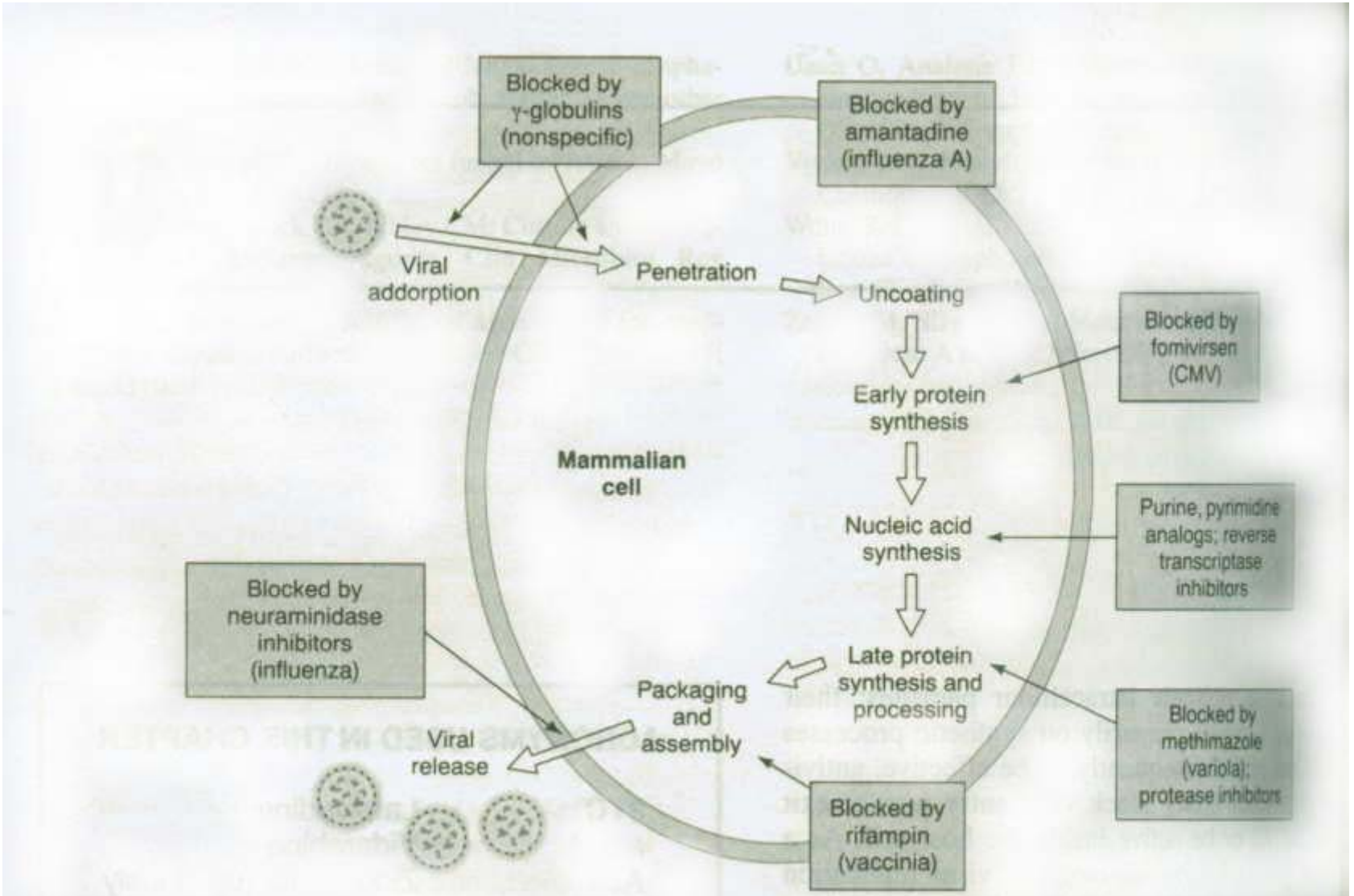


Figure 49–1. The major sites of antiviral drug action. (Modified and reproduced, with permission, from Katzung B, Trevor AT [editors]: *Pharmacology: Examination & Board Review*, 4th ed. Originally published by Appleton & Lange. Copyright © 1995 by The McGraw-Hill Companies, Inc.)

Viral replication

- Viral attachment & entry
- Penetration
- Uncoating
- Early protein synthesis
- Nucleic acid synthesis
- Late protein synthesis & processing
- Packaging & assembly
- Viral release

Viral Replication

- Recognise host surface proteins & get attached
- Virusus penetrates the host cell membrane by endocytosis
- Envelope merges with the host cell membrane
- Capsid along with genome enters the interior of cell
- Capsid removed within the cell, to free the genome containing DNA

- Viral genome enters the cell nucleus & its DNA is transcribed into viral m-RNA by the host cell's RNA polymerase.
- Host cell's ribosomes then utilise the viral m-RNA for the synthesis of viral proteins and enzymes.
- During this process ,**regulatory proteins** are synthesised first ,which initiate the transcription of early genes responsible for viral DNA replication by **viral DNA-polymerase**.

- After DNA replication late genes are transcribed & translated to produce **structural proteins** required for assembly of new virions.
- Viral components are then **assembled** to form a mature virus particle.
- **Release** of progeny virus takes place through **budding** of host cell.

C/F OF ANTIVIRAL DRUGS

- **DNA POLYMERASE INHIBITORS –**
- **PURINE ANALOGUES-**
- ACYCLOVIR VALACYCLOVIR
- GANCICLOVIR VALGANCICLOVIR
- FAMCICLOVIR PENCICLOVIR
- CIDOFOVIR ADEFOVIR
- ENTECAVIR VIDARABINE
- **PYRIMIDINE ANALOGUES –**
- IDOXURIDINE , TRIFLURIDINE, TELBIVUDINE
- **NON-NUCLEOSIDES -** FOSCARNET

- **m-RNA SYNTHESIS INHIBITORS**
- RIBAVIRIN ,FOMIVIRSEN
- **INHIBITORS OF VIRAL PENETRATION & UNCOATING**
- AMANTADINE, RIMANTADINE,DOCOSANOL
- **NEURAMINIDASE INHIBITORS**
- ZANAMIVIR , OSELTAMIVIR ,PERAMIVIR
- **IMMUNOMODULATORS**
- INTERFERONS, PALIVIZUMAB , IMIQUIMOD
- **ANTI-RETROVIRAL DRUGS**

Drugs for Herpes Simplex Virus(HSV) & Varicella-Zoster infection

- **Acyclovir**
- **Valacyclovir**
- **Famciclovir**
- Acyclovir is only one available for I/V use.
- Valacyclovir & Famcyclovir -Superior for Herpes zoster
- Not indicated in varicella

Acyclovir

- HSV-1 , HSV-2 , VZV
- **INDICATIONS –**
- **Skin infections** – Initial & recurrent labial & genital herpes (as a cream) , most effectively when new lesions are forming . For Skin & m.m. infections _ as tablets or oral suspensions.
- **Ocular keratitis** – as ointment
- **Prophylaxis & Treatment in immunocompromised-** Oral, tab, suspension,
- **Encephalitis , disseminated disease**

Acyclovir

- **V-Z viruses**
- **Chicken-pox** -
- immunocompromised (i.v.) ,
- immunocompetent with pneumonitis , hepatitis
- **Shingles** –
- in immunocompetent , tab/suspension within 48 hrs of appearance of rash
- In immunocompromised – i.v.
- **Oral & topical 5 times a day.**

- **Mechanism:**
  - Three phosphorylation steps for activation.
    - First converted to the monophosphate derivative by the ***virus-specified*** **thymidine kinase;** （selective activation）
    - Then to the di- and triphosphate compounds by *host's* cellular enzymes .
  - Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms:
    - Inhibition of **viral DNA polymerase**, with binding to the DNA template as an irreversible complex ;
    - Incorporation into the viral DNA → chain termination

ADRs

- Gen. well tolerated
- N/D , Headache
- I/V - Extravasation – local inflammation
- Reversible renal dysfunction
- Neurologic toxicity

Valacyclovir

- Prodrug of acyclovir
- Oral bioav. 54 % , given 8 hrly
- **Use** –
- genital herpes
- Oro-labial herpes
- **S/Es** – N/V , rash, dizziness , liver enzyme elevation , anemia , neutropenia , confusion , hallucinations , seizures.

Cytomegalovirus

- In advanced immunosuppression
- Reactivation of latent infection
- End organ disease – Retinitis , Colitis , esophagitis, CNS ds . & pneumonitis
- AIDS & organ transplantation
- **GANCICYCLOVIR**
- **VALGANCICLOVIR**
- **FOSCARNET**
- **CIDOFOVIR**

GANCICLOVIR

- SIMILAR TO ACYCLOVIR IN ITS MODE OF ACTION BUT MUCH MORE TOXIC.
- I/V OR ORALLY , ELIMINATED IN URINE , UNCHANGED .
- HALF LIFE – 4 HRS .
- I.V. USE IS LIMITED TO – LIFE OR SIGHT – THREATENING CMV INFECTION IN IMMUNO-COMPROMISED PTS.

GANCICLOVIR

- ORAL – FOR MAINTENANCE OF SUPPRESSIVE TREATMENT OF RETINITIS IN PTS WITH AIDS.
- TO PREVENT CMV DISEASE IN PATIENTS WHO ARE IMMUNO-COMPROMISED & FOLLOWING ORGAN TRANSPLANTATION .
- **ADRs** – NEUTROPENIA ,THROMBOCYTOPENIA, FEVER, RASH,GI SYMPTOMS ,CONFUSION & SEIZURE .

FOSCARNET

- I.V. FOR RETINITIS DUE TO CMV IN PATIENTS WITH HIV INFECTION (WHEN GANC. C/I)
- ACYCLOVIR –RESISTANT HSV INFECTION
- **S/Es** – RENAL TOXICITY , N/V , NEUROLOGICAL REACTIONS, MARROW SUPPRESSION

FOMIVIRSEN

- AN OLIGONUCLEOTIDE
- **ANTI-CMV AGENT**
- **BINDS TO m-RNA –INHIBITS THE SYNTHESIS OF IMMEDIATE EARLY PROTEINS NEEDED FOR VIRAL REPLICATION**
- RESISTANCE LEAST COMMON
- SELECTIVE ACCUMULATION IN RETINA & VITREOUS HUMOUR
- INJECTED INTRAVITREALLY FOR CMV RETINITIS IN AIDS PATIENTS
- **S/Es-** IRITIS,VITREITIS,INCREASED INTRAOCULAR PRESSURE

TRIFLURIDINE

- PYRIMIDINE NUCLEOSIDE.AGAINST HSV-1 , HSV-2 , VACCINIA , AND SOME ADENOVIRUSES.
- INCORPORATION OF TRIFLURIDINE TRIPHOSPHATE INTO BOTH VIRAL AND CELLULAR DNA PREVENTS ITS SYSTEMIC USE.
- **THERAPY FOR KERATO-CONJUNCTIVITIS AND FOR RECURRENT EPITHELIAL KERATITIS DUE TO HSV-1 AND HSV-2.**
- **TOPICAL APPLICATION**, ALONE OR IN COMBINATION WITH INTERFON ALFA, HAS BEEN USED SUCCESSFULLY IN TREATMENT OF **ACYCLOVIR-RESISTANT HSV INFECTIONS.**

IDOXURIDINE

- INHIBITION OF VIRAL DNA POLYMERASE → BLOCKS DNA SYNTHESIS.
- NO EFFECT ON RNA VIRUS.
- **ONLY TOPICAL APPLICATION** BECAUSE OF ITS GREATER SIDE EFFECTS IN SYSTEMIC APPLICATION.
- TREATMENT OF OCULAR OR DERMAL INFECTIONS DUE TO HERPES VIRUS , ESPECIALLY ACUTE EPITHELIAL KERATITIS DUE TO HERPES VIRUS.

VIDARABINE

- ADENINE NUCLEOSIDE ANALOGUE
- AGAINST HSV, VZV, CMV, HBV AND SOME RNA VIRUSES.
- PHOSPORYLATED INTRACELLULAR BY HOST ENZYMES TO FORM VIDARABINE TRIPHOSPHATE & INHIBITS VIRAL DNA POLYMERASE
- ACTS AS DNA CHAIN TERMINATOR
- BUT INCORPORATED INTO BOTH VIRAL AND CELLULAR DNA → EXCESSIVE TOXICITY

VIDARABINE

- RAPIDLY METABOLIZED TO HYPOXANTHINE ARABINOSIDE.
- INSTABILITY AND TOXICITY LIMITED ITS CLINICAL UTILITY.
- **ONLY TOPICAL USE - IN HSV KERATO- CONJUCTIVITIS, SUPERFICIAL KERATITIS IN PTS NOT RESPONSIVE TO IDOXURIDINE.**
- **S/E-** LACRIMATION,IRRITATION,PHOTOPHOBIA

RIBAVIRIN

- GUANOSINE ANALOG.
- PHOSPHORYLATED INTRACELLULARLY BY HOST CELL ENZYMES.
- MECHANISM: **TO INHIBIT THE VIRAL RNA-DEPENDENT RNA POLYMERASE OF CERTAIN VIRUSES**
- RIBAVIRIN TRIPHOSPHATE INHIBITS THE REPLICATION OF A WIDE RANGE OF DNA AND RNA VIRUSES, INCLUDING INFLUENZA A AND B, PARAINFLUENZA, RESPIRATORY SYNCYTIAL VIRUS, PARAMYXOVIRUSES, HCV , AND HIV-1.

RIBAVIRIN

- Oral absorption is rapid,first pass extensive,yet oral bioav. 65%
- Also given as aerosol to treat influenza & infections due to respiratory syncytial virus
- i.v. to reduce mortality in lassa fever (arena)
- Highly effective ag. Influenza –A & B viruses.
- Oral ribavirin & s.c. interferon-alpha -2b is synergistically effective ag. Hepatitis –C.

ANTI-HEPATITIS AGENTS

- **INTERFERONES –**
- RELEASED BY HOST CYTOKINES
- COMPLEX ANTI-VIRAL,IMMUNOMODULATORY
- ANTI-PROLIFERATIVE ACTIVITIES
- α , β , γ according to antigenic & physical properties .

- **INF-α** – synthesised primarily by human leukocytes
- **INF –β** - from fibroblasts
- **INF –γ** - which is a lymphokine , is produced by T-lymphocytes as a part of the immune response to viral and non-viral antigens .
- Commercial synthesis of IFNs is done by recombinant DNA tech.in bacterial cultures.
- **INF –α & β exert potent antiviral effects**
- **IFN – γ has antiviral & immunomodulatory effects.**

BINDING TO SPECIFIC CELL MEMBRANE RECEPTORS & AFFECT VIRAL REPLICATION AT MULTIPLE STEPS -

- INHIBITION OF VIRAL PENETRATION,UNCOATING
- INHIBITION OF TRANSLATION –
- INHIBITION OF TRANSCRIPTION ,PROTEIN PROCESSING ,MATURATION & RELEASE
- INCREASED EXPRESSION OF MHC-antigen
- ACTIVATION OF MACROPHAGES & NATURAL KILLER CELLS ALONG WITH MODULTION OF CELL SURFACE PROTEINS TO FASCILITATE IMMUNE RECOGNITION

- ALL DNA & RNA VIRUSES ARE SENSITIVE TO IFNs
- ENDOGENOUS IFNs ARE RESPONSIBLE FOR MAKING MOST VIRAL INFECTIONS SELF-LIMITING.
- IFNS CAN BE ADMINISTERED S.C., I.M. ,I.V., OR INTRA-LESIONALLY
- DO NOT CROSS BBB
- ELIMINATED THROUGH PHAGOCYTOSIS OR BY KIDNEY/LIVER.

CLINICAL USES

- **IFN –α -2a** –chronic hepatitis –B infection , AIDS related Kaposi's sarcoma ,chronic hepatitis–C, hairy cell leukemia & chronic myelogenous leukemia
- **IFN –α -2b** (s.c., i.m.) –Hepatitis –C ,malignant melanoma , condyloma acuminata , chronic hepatitis –B , chronic hepatitis –C and non-hodgkin's lymphoma
- As an adjunt in treatment of viral infections including AIDS .

- **S/Es** – flu –like syndrome – Headache , fever , chills , myalgias , malaise , transient hepatic enzyme elevation.
- Chronic therapy – neurotoxicities , myelosuppression , profound fatigue , wt.loss , rash , cough , myalgia , alopecia , tinnitus, hepatic and thyroid dysfunction .

Lamivudine

- Cytosine analogue
- Inhibits HBV DNA polymerase
- Inhibits HIV reverse transcriptase by competing with deoxycytidine triphosphate for incorporation into viral DNA
- Resulting in chain termination .
- Against HIV-1 , synergistic with a variety of antiretroviral nucleoside analogs, including zidovudine and stavudine.
- Treatment of chronic hepatitis B infection.

- oral bioavailability > 80 %
- Not food dependent
- The majority of lamivudine is eliminated unchanged in the urine.
- Excellent safety profile
- Headache , nausea , dizziness,
- Co-infection with HIV – risk of pancreatitis .

Anti-influenza agents

- Amantadine & Rimantadine
- Zanamivir & Oseltamivir

Amantadine

- Inhibits uncoating of viral RNA within infected host cells
- Inhibits replication of Influenza A
- **A proton ion channel M2 of the viral membrane is the target .**
- **Inhibition of M2 protein – prevention of H+ mediated dissociation of ribonucleoprotein core segment (a prerequisite for viral replication)**
- Well absorbed orally
- Excreted unchanged in urine over 2-3 days
- Half life 16 hours

Rimantadine

- 4-10 times more active than amantidine
- Better tolerated, longer acting , more potent.
- Dose reduction required for both in – elderly & in patients with renal insufficiency .
- For rimantadine – in patients with marked hepatic insufficiency also .

- **S/Es** – generally well tolerated
- Nausea , Anorexia , insomnia , dizziness, nightmares , lack of mental conc. , hallucinations, postural hypotension, ankle edema .
- **Uses** – prophylaxis of Influenza A2
- Treatment of influenza A2
- Parkinsonism
- C/I – Epilepsy & other CNS ds, gastric ulcer , pregnancy

Zanamivir & Oseltamivir

- **Neuraminidase inhibitors**
- Interfere with the release of progeny influenza virus from infected – new host cells
- (Neuraminidase enzyme required for release)
- Preventing the spread of infection in respiratory tract
- Activity ag. Both Infl.A & Infl. B

- Zanamivir is given through inhalation
- 5-15 % of total dose is absorbed & excreted in the urine .
- S/Es ˍ Cough , brochospasm , reversible decrease in pulmonary function & transient nasal & throat discomfort .

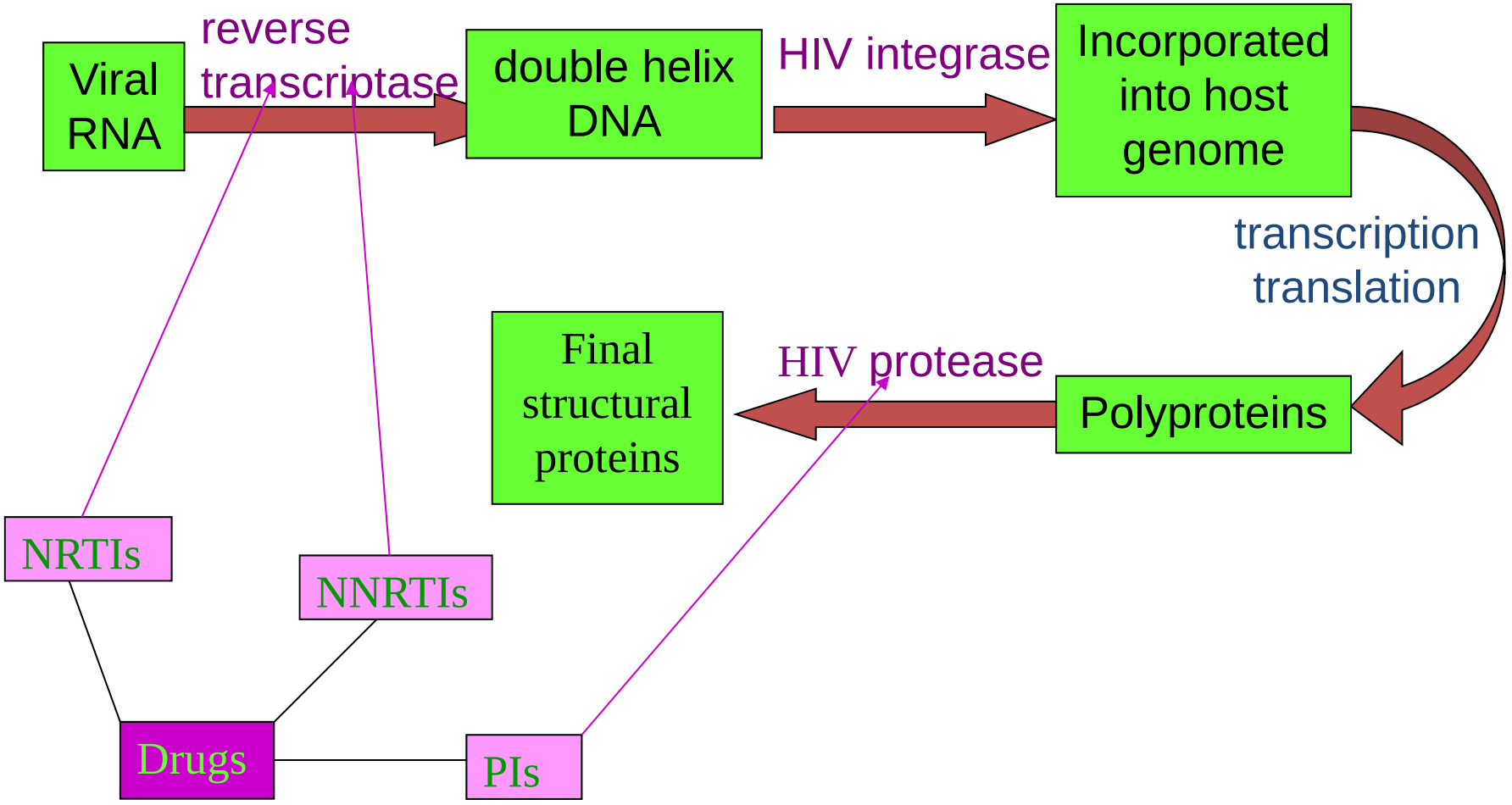
Oseltamivir

- is orally given
- A prodrug
- Activated by hepatic esterases
- Widely distributed throughout the body
- Headache , fatigue & diarrhea.
- **AVIAN INFLUENZA**

PERAMIVIR

- FOR EMERGENCY TREATMENT OF HOSPITALISED PATIENTS WITH H1N1 INFLUENZA
- ORAL BIOAV. POOR
- USED FOR PATIENTS SHOWING RESISTANCE TO OSELTAMIVIR OR TO ZANAMIVIR INHALATION
- USED AS THE ONLY I/V OPTION FOR TREATING SWINE FLU
- CLEARED PHASE III

Anti-Retroviral(Anti-HIV) Agents


Viral RNA
reverse transcriptase
double helix DNA
HIV integrase
Incorporated into host genome
transcription
translation
Polyproteins
HIV protease
Final structural proteins
NRTIs
NNRTIs
Drugs
PIs

- Surface proteins gP120 , linked to a transmembrane stalk (gP41)
- Antigenic & fascilitate viral attachment to CD4 cells of T lymphocytes
- Core genome contains RNA along with 3 genes **: gag, pol, env**
- Gag & pol code for formation of reverse transcriptase, integrase & protease enzymes
- Env genes code for the formation of envelope proteins gP120 & gP41.

- Integrated into host genome by **viral enzyme integrase**
- Provirus DNA transcribed into new genomic RNA & m-RNA
- m-RNA translated into viral proteins by host ribosomes
- Assembly of virion
- Maturation in which **viral protease** enzyme cleaves the polypeptide into functional structural proteins & viral enzymes.
- Budding & Release to infect other cells

- **Prime target – Helper T-lympocytes ,which have CD4 expressed on their surface.**
- gP120 binds to CD4 & to Chemokine co-receptors (CXCR4), (CCR5 for macrophages)
- Gp 41 causes **fusion** of viral envelope with plasma membrane of T-cells .
- After fusion ,virus **enters** the target cells.
- Uncoating
- Viral **reverse transcriptase** synthesises DNA from viral RNA.

C/F OF ANTI-HIV DRUGS

- **Nucleoside Reverse Transcriptase Inhibitors(NRTIs)**
- Zidovudine
- Stavudine
- Lamivudine
- Abacavir
- Zalcitabine
- Emtricitabine
- Didanosine

- **Non-nucleoside Reverse transcriptase inhibitors (NNRTIs) –**
- Efavirenz
- Nevirapine
- Delavirdine
- Etravirine
- **Nucleotide Reverse transcriptase inhibitors –**
- Tenofovir

- **Protease Inhibitors (PIs) –**
- Saquinavir
- Indinavir
- Nelfinavir
- Amprenavir
- Fosamprenavir
- Ritonavir
- Lopinavir

- **Entry/fusion Inhibitors**
- Enfuvirtide

- **CCR5 Inhibitors**
- Maraviroc

- **Integrase Inhibitors**
- Raltegravir

Nucleoside Reverse Transcriptase Inhibitors

Mechanism of Action

① Competitive inhibition of HIV-1 reverse transcriptase ;

② Incorporated into the growing viral DNA chain → cause termination

- Drugs requires intracytoplasmic activation---phosphorylation → triphosphate form
- Most have activity against HIV-2 as well as HIV-1.

Zidovudine

- Azidothymidine AZT
- Deoxythymidine analog
- anti-HIV-1 and HIV-2
- Well absorbed from the gut and distributed to most body tissues and fluids, including the cerebrospinal fluid.
- Eliminated primarily by renal excretion following glucuronidation in the liver.

- Decreases the rate of clinical disease progression and prolongs survival.
- Reduces the rate of vertical (mother-to-newborn) transmission of HIV.
- Begin b/w 14-34 weeks
- In neonate , birth to 6 weeks of age.
- Also used for post-exposure prophylaxis for health-care workers.
- Adverse effect: myelosuppression→ anemia or neutropenia; gastrointestinal intolerance, headache, insomnia, myopathy

- Less frequent – thrombocytopenia, hyperpigmentation of nails

- Interactions – increased serum levels of – Probenecid, Phenytoin, Fluconazole, valproic acid, lamivudine.

Zalcitabine (ddC)

- Cytosine analogue
- Anti-HIV-1
- Zalcitabine + Zidovudine + one protease inhibitor
- Suitable for patients intolerant to or resistant to ziduvidine .
- Long intracellular half-life of 10 hrs.
- Dose-dependent peripheral neuropathy. Contraindication to use with other drugs that may cause neuropathy.
- Stomatitis & esophageal ulceration

Stavudine(d4T)

- Thymidine analog (d4T), not used with AZT because AZT may reduce the phosphorylation of d4T.
- Anti-HIV-1 and HIV-2
- High oral bioavailability (86%) that is not food-dependent.
- Plasma protein binding is negligible, mean cerebrospinal fluid concentrations are 55% of those of plasma.
- Excretion is by active tubular secretion and glomerular filtration.

- USED FOR THE THERAPY OF HIV INFECTIONS AS A PART OF MULTIDRUG REGIMEN & ALSO FOR POST EXPOSURE PROPHYLAXIS
- **ADVERSE EFFECTS**:
  - DOSE-LIMITING TOXICITY IS A DOSE-RELATED PERIPHERAL SENSORY NEUROPATHY.
  - PANCREATITIS, ARTHRALGIAS , ELEVATION IN SERUM AMINO-TRANSFERASES.

Didanosine (ddI)

- SYNTHETIC ANALOG OF DEOXY-ADENOSINE
- PLASMA PROTEIN BINDING IS LOW (<5%), CEREBROSPINAL FLUID CONCENTRATIONS ARE 20% OF SERUM CONCENTRATIONS.
- ELIMINATED BY GLOMERULAR FILTRATION AND TUBULAR SECRETION.
- ADMINISTERED IN COMBINATION DUE TO RESISTANCE
- SHOULD BE TAKEN ON AN EMPTY STOMACH.
- FQS AND TETRACYCLINS SHOULD BE GIVEN AT LEAST 2 HRS BEFORE OR AFTER DDI TO AVOID DECREASED ANTIBIOTIC CONC. DUE TO CHELATION .

- ADVERSE EFFECTS:
  - DOSE-DEPENDENT PANCREATITIS
  - PAINFUL PERIPHERAL DISTAL NEUROPATHY
  - DIARRHOEA
  - HEPATITIS
  - ESOPHAGEAL ULCERATION
  - CARDIO-MYOPATHY
  - CENTRAL NERVOUS SYSTEM TOXICITY (HEADACHE, IRRITABILITY, INSOMNIA)

Non-nucleoside reverse transcriptase inhibitors

- Including ***delavirdine, nevirapine, efavirenz*.**
- Bind directly to a site on the viral reverse transcriptase that is near to but distinct from the binding site of the NRTIs.
- Neither compete with nucleoside triphosphates nor require phosphorylation to be active.
- The binding to the enzyme's active site results in **blockade of RNA- and DNA-dependent DNA polymerase activities.**

- Specific activity against HIV-1.
- Cross-resistance among this class of agents.
- The rapid emergence of resistance prohibits mono-therapy with any of the NNRTIs.
- No cross-resistance between the NNRTIs and the NRTIs or the protease inhibitors.
- Oral bioavailability is high.
- Metabolized by the CYP3AP 450 isoform, excreted in the urine.
- Adverse effects: skin rash, elevation in liver enzymes

NEVIRAPINE

- As a combination of multidrug anti-retroviral therapy .
- 200 mg/day oral is effective in preventing vertical transmission (given at the time of labour); single dose of 2mg/kg oral dose to be given to the neonate within 3 days after birth.
- Half life 25-30 hrs.

EFAVIRENZ

- Used as post-operative prophylaxis.
- 600mg orally OD.
- S/Es involve CNS : dizziness, nightmares, insomnia , headache & euphoria
- Other S/Es – skin rash, nausea, vomiting, elevated liver enzymes and serum cholesterol levels.
- teratogenic

DELAVIRDINE

- Used for treatment of HIV-1 infection as a part of combination therapy.
- Dose 400 mg TDS
- If didanosine or antacids are to be used, its dosing to be withheld by 1 hr as they decrease its oral bioavailability.
- Metabolised by and inhibits CYP3A4 & thus increases the plasma conc. of several protease inhibitors such as amprenavir , indinavir , lopinavir, ritonavir, saquinavir.
- Dose reduction of these required.

NtRTIs

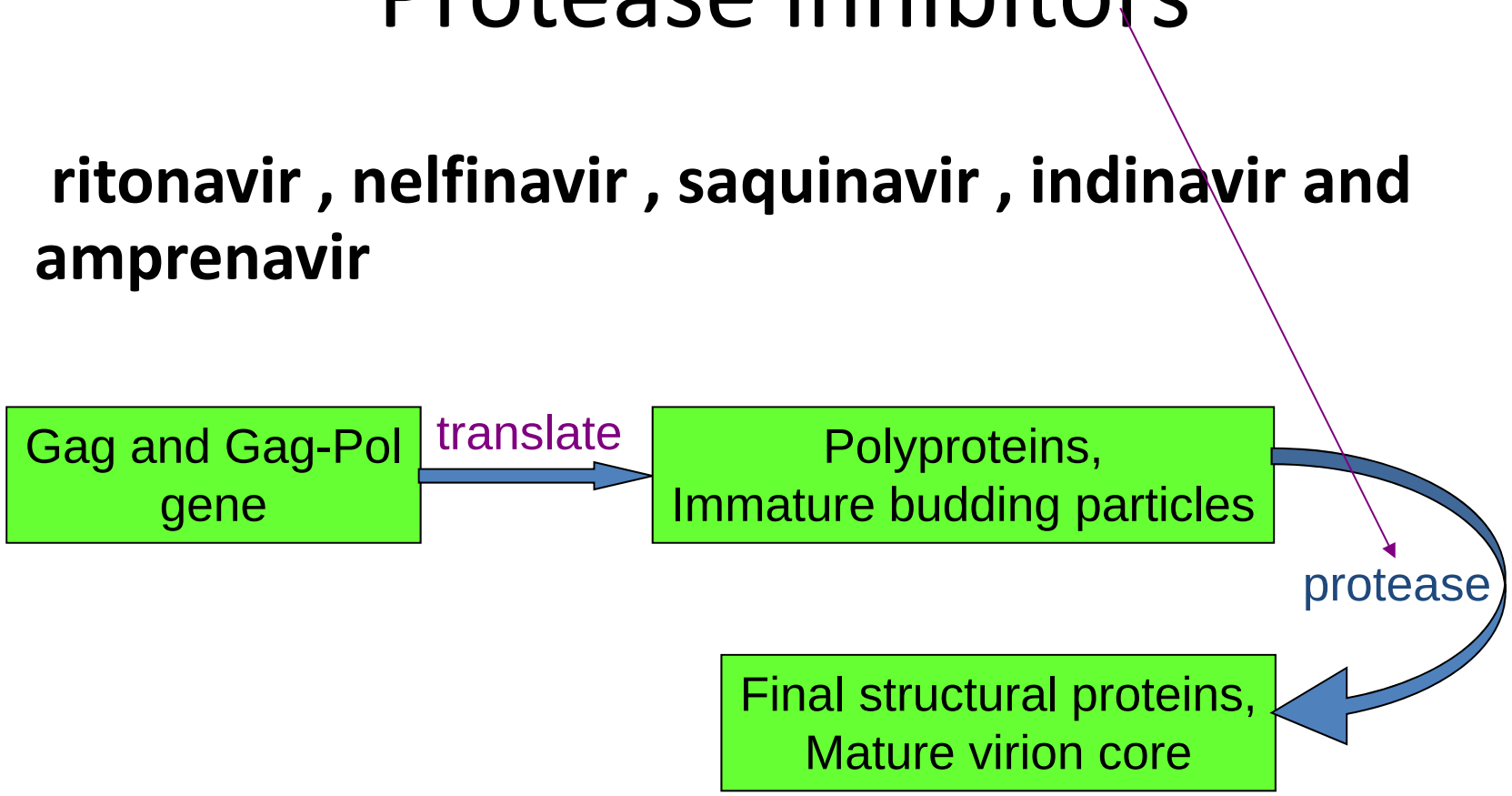
Tenofovir

- Available as tenofovir disproxil fumarate
- Prodrug, first hydrolysed in liver to tenofovir
- Which is subsequently phosphorylated to an active tenofovir **diphosphate** (that is the active form)
- inhibits HIV reverse transcriptase enzyme
- Causes termination of chain elongation after getting incorporated into viral DNA
- Analogue of adenosine 5 monophosphate

- Used along with other anti-HIV drugs in the treatment of HIV in a dose of 300 mg once daily after meals.
- Oral bioavailability with meals 40 %
- Usually well tolerated
- Nausea, Vomiting, diarrhoea and osteomalacia
- Hepatomegaly, pancreatitis, lactic acidosis
- Increases the plasma levels of didanosine leading to toxicity .

Protease inhibitors

ritonavir , nelfinavir , saquinavir , indinavir and amprenavir



- Protease is responsible for cleaving precursor molecules to produce final structural proteins of mature virion core .
- By preventing cleavage , PIs result in the production of immature , noninfectious viral particles .

- Combination therapy with PIs and other antiretroviral drugs significantly improves the efficacy by blocking HIV replication at different stages in intracellular life cycle.
- Cross resistance between indinavir and ritonavir can occur.

S/Es

- A syndrome of redistribution & accumulation of body fat that results in central obesity , dorso-cervical fat enlargement & a cushingoid apperance is seen with PIs.
- Increase in triglyceride, LDL levels along with glucose intolerance & insulin resistance
- Increase in spontaneous bleeding in patients with hemophilia A & B.
- Drug interactions due to enzyme induction & inhibition.

Drug interactions

- Competitive inhibitors of drugs metabolised by CYP3A4 family
- Life threatening toxicities with-
- Cisapride (arrythmias),
- ergot alkaloids (vasospasm)
- Statins (rhabdomyolysis)
- Midazolam (resp.depression)
- Enzyme inducers may decrease plasma levels of PIs.

Fusion Inhibitors

ENFUVERTIDE

- Blocks entry into cell
- Binds to gp41 subunit of viral envelope glycoprotein
- Prevents conformational changes required for fusion of viral & cellular membranes.
- Metabolism by hydrolysis
- Without involvement of CYP450
- Elimination half life 3-8 hrs

S/Es

- Most common s/e is – local injection site reactions
- H/S
- Eosinophilia & pneumonia like manifestations.

Chemokine receptor -5 antagonists

Maraviroc

- Binds to CCR5 receptors on CD4 cell membrane & prevents the entry of the virus into the host cell
- Used along with other antiretrovirals ,in highly resistant adult patients
- Main s/e hepatotoxicity
- Others –cough,rash,fever,muscular pain,GIT distress

Integrase inhibitors (Raltegravir)

- Inhibits the viral enzyme integrase , thereby preventing the insertion of HIV genetic material into chromosomes of host cells & halting the viral replication process
- Not metabolised by Cytochrome P-450 system
- Drug interactions are not clinically significant
- Rifampicin decreases raltegravir levels
- Antacids and iron bind to integrase ,hence dosing should be separated by 2hrs.
- Usual oral dose 200 mg BD orally
- S/Es- nausea,diarrhea,fever,headache,myopathy.

HAART

- Highly Active Antiretroviral Therapy
- **Combination of NRTIs & Protease inhibitors , working with different mechanisms , combined drugs produce a sequential blockade of viral reproduction at two different steps . HIV can not develop mutants simultaneously to different drugs working by two different mechanisms.**
- **Popular combination choices-**
- 2 NRTIs+ 1 NNRTI or One /two protease inhibitors i.e.
- NRTIs (2) +PI (1) or
- NRTIs (2) + NNRTI (1) or
- NRTIs(2) +PI (1) +Ritonavir(PI)

- **Preffered drug regimens are-**
- Zidovudine + Lamivudine + efavirenz
- Zidovudine + Lamivudine + Lopinavir/ritonavir
- **Alternatives –**
- **NRTI (1)+ NNRTI (1) + PI (1) OR**
- **NRTI(1) + NNRTI (1)+ PI(2)**