		Overview of		
Enconholitio/	Vir	al infectior	າຣ	
Encephantis/_	Common cold—		Eve	infections
	- Rhinoviruses		- He	erpes simplex virus
- Mossles	- Parainfluenza vi		- Ac	lenovirus
	- Respiratory syn	cvtial	- C\	tomegalovirus
- LCIVI VIIUS	virue	Cytian Contraction	رى	ternegale mae
- Arbovirus	VIIUS		–Parotitis	<i>⊢</i> Pneumonia
- Rables		7	- Mumps/	- Influenza virus,
Pharyngitis	Gingivostomatit	tis	virus /	Types A and B
- Adenovirus	<ul> <li>Herpes simplex</li> </ul>	type 1		- Parainfluenza
- Epstein-Barr v	virus	ALA		virus
- Cytomegalovirus				- Respiratory
eyternegenetin		EBN 20-		syncytial virus
Cardiovascula	r —	<u>8925511</u>		- Adenovirus
- Coxsackie B v	/irus			- SARS coronavirus
		A A A A A		
Hepatitis ——		- 16 1 20 K	3/20	—— Mvelitis
<ul> <li>Hepatitis viru</li> </ul>	S			- Poliovirus
types A, B, C	, D, E			- HTI V-I
Skin infaction		·.·	$\sim$	
Variable zost	S virus			Gastroontoritis
		······································		
- Human herpe	svirus o		Con la constante	- Adenovirus
- Smallpox	ntagiogum	A flat the		Norovirus
	amayirua	Sexually transmitted	$\backslash$	
- numan papilio	onavirus	diseases	$\backslash$	- Astrovirus
- Parvovirus B	19	- Hernes simpley type	2	- Coronavirus
		- Human papillomaviru		Pancreatitis
			3	- Coxsackie B virus
- Coxsackie A	virus	- 1 11 V		

- Coxsackie A virus

Understanding Viruses They are different from other Microbes

#### **Viral replication**

- A virus cannot replicate on its own
- It must attach to and enter a host cell
- It then uses the host cell's energy to synthesize protein, DNA, and RNA

### **Understanding Viruses**

Viruses are difficult to kill because they live inside the cells

 Any drug that kills a virus may also kill cells



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### Antivirals

available for many viral infections

Viruses controlled by current antiviral therapy

- Cytomegalovirus (CMV)
- Hepatitis viruses
- Herpes viruses
- Human immunodeficiency virus (HIV)
- Influenza viruses (the "flu")
- Respiratory syncytial virus (RSV)

- Viruses have no cell wall and made up of nucleic acid components
- Viruses containing envelope antigenic in nature
- Viruses are obligate intracellular parasite
- They do not have a metabolic machinery of their own – uses host enzymes

- Certain viruses multiply in the cytoplasm but others do in the nucleus
- Most multiplication take place before diagnosis is made



- Many antiviral drugs are *Purine or Pyrimidine analogs*.
- Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active.
- Anti-viral agents inhibits active replication so the viral growth resumes after drug removal.

#### Antivirals how they act Key characteristics of antiviral drugs

□ Able to enter the cells infected with virus

□ Interfere with viral nucleic acid synthesis and/or regulation

□ Some drugs interfere with ability of virus to bind to cells

□ Some drugs **stimulate the body's immune system** 

□ Best responses to antiviral drugs are in patients with competent immune systems

A healthy immune system works synergistically with the solution of suppress viral activity

### **Antiviral Medications**

#### **Antiviral drugs**

 $\square$  Used to treat infections caused by viruses other than HIV

#### **Antiretroviral drugs**

Used to treat infections caused by HIV, the virus that causes AIDS

#### **Herpes-Simplex Viruses**

- □ HSV-1 (oral herpes)
- □ HSV-2 (genital herpes)

#### **Varicella Zoster Virus**

- Chickenpox
- **Shingles**



### **Antiviral Drugs: Nonretroviral**

#### □ Mechanism of action

Inhibit viral replication

#### Used to treat non-HIV viral infections

- Influenza viruses
- HSV (herpes simplex virus), VZV (vericella zoster virus)
- CMV (cytomegalovirus)
- Hepatitis A, B, C (HAV, HBV, NCV)

#### **Adverse Effects**

- □ Vary with each drug
- <sup>1</sup> Healthy cells are often killed also, resulting in serious toxicities

- Current anti-viral agents do not eliminate non-replicating or latent virus
- Effective host immune response remains essential for the recovery from the viral infection
- Clinical efficacy depends on achieving inhibitory conc. at the site of infection within the infected cells

#### Stages of viral replication

• Cell entry – attachment

- penetration

- Uncoating
- Transcription of viral genome
- Translation
- Assembly of virion components
- Release





**Anti-viral drugs** Anti-herpes virus agents

- Acyclovir / Valacyclovir
- Famciclovir / Penciclovir
- Ganciclovir / Cidofovir
- Foscarnet
- Trifluridine / Idoxuridine / Vidarabine

#### Acyclovir & Congeners :

- Valacyclovir is a prodrug of Acyclovir with better bioavailability.
- Famciclovir is hydrolyzed to Penciclovir and has greatest bioavailability.
- Penciclovir is used only topically whereas Famciclovir can be administered orally.

#### PHARMACOLOGY OF ACYCLOVIR AND CONGENERS

 Acyclovir, Valacyclovir, Ganciclovir, Famciclovir, Penciclovir all are guanine nucleoside analogs.



# Mechanism of action of Acyclovir and congeners :

- All drugs are phosphorylated by a viral thymidine-kinase, then metabolized by host cell kinases to nucleotide analogs.
- The analog inhibits viral DNApolymerase
- Only actively replicating viruses are inhibited

- Acyclovir is thus selectively activated in cells infected with herpes virus.
- Uninfected cells do not phosphorylate
   11/18 acyclovir.



#### **Mechanism of Action of Acyclovir**



(a) Acyclovir structurally resembles the nucleoside deoxyguanosine.



(b) The enzyme thymidine kinase combines phosphates with nucleosides to form nucleotides, which are then incorporated into DNA.



(c) Acyclovir has no effect on a cell not infected by a virus, that is, with normal thymidine kinase. In a virally infected cell, the thymidine kinase is altered and converts the acyclovir (which resembles the nucleoside deoxyguanosine) into a false nucleotide—which blocks DNA synthesis by DNA polymerase.

#### **Antiviral 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

**Pharmacokinetics of Acyclovir :** 

- Oral bioavailability ~ 20-30%
- Distribution in all body tissues including CNS
- Renal excretion: > 80%
- Half lives: 2-5 hours
- Administration: Topical, Oral, IV

#### Adverse effects of Acyclovir / Ganciclovir

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

#### Therapeutic uses :

#### Acyclovir is the drug of choice for:

- HSV Genital infections
- HSV encephalitis
- HSV infections in immunocompromised patient

#### Ganciclovir is the drug of choice for:

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

#### Cidofovir :

- It is approved for the treatment of **CMV** retinitis in immunocompromised patients
- It is a nucleotide analog of cytosine no phosphorylation required.
- It inhibits viral DNA synthesis
- Available for IV, Intravitreal inj, topical
- Nephrotoxicity is a major disadvantage.

### **Anti-viral drugs** PHARMACOLOGY OF VIDARABINE

 Vidarabine is a nucleoside analog. (adenosine)

## Antiviral spectrum of Vidarabine : HSV-1, HSV-2 and VZV.

Its use is limited to HSV keratitis only

#### Vidarabine

- The drug is converted to its triphosphate analog which inhibits viral DNApolymerase.
- Oral bioavailability ~ 2%
- Administration: Ophthalmic ointment
- Used in HSV keratoconjunctivitis in immunocompromised patient.
- Anemia and SIADH are adverse effects.

#### PHARMACOLOGY OF TRIFLURIDINE

• Trifluridine is a Pyrimidine nucleoside analogs - inhibits viral DNA synthesis.

#### Antiviral spectrum Trifluridine :

- HSV-1, HSV-2 and VZV.
- Use is limited to Topical Ocular HSV Keratitis

#### PHARMACOLOGY OF FOSCARNET

- Foscarnet is an inorganic pyrophosphate analog
- It directly inhibits viral DNA and RNA -polymerase and viral inverse transcriptase (it does not require phosphorylation for antiviral activity)

#### Foscarnet

- HSV-1, HSV-2, VZV, CMV and HIV.
- Oral bioavailability ~ 10-20%
- Distribution to all tissues including CNS
- Administration.Rad

#### **Adverse effects of Foscarnet**

- Hypocalcemia and hypomagnesemia (due to chelation of the drug with divalent cations) are common.
- Neurotoxicity (headache, hallucinations, seizures)
- Nephrotoxicity (acute tubular nephrosis, interstitial nephritis)

**Therapeutic uses of Foscarnet** 

- It is an alternative drug for
- HSV infections (acyclovir resistant / immunocompromised patient )
- CMV retinitis (ganciclovir resistant / immunocompromised patient )

#### Respiratory viral infections Influenza –

- Amantadine / Rimantadine
- Oseltamivir / Zanamavir (Neuraminidase inhibitors)
   RSV bronchiolitis –



- Amantadine and Rimantadine : Influenza
- Prevention & Treatment of influenza A
- Inhibition of viral uncoating by inhibiting the viral membrane protein M2
- Influenza A virus
- Amantadine has anti-parkinsonian

Pharmacokinetics of Amantadine

- Oral bioavailability ~ 50-90%
- Amantadine cross extensively BBB whereas Rimantadine does not cross extensively.
- Administration: Oral

#### Neuraminidase inhibitors : Influenza Oseltamivir / Zanamavir

- Influenza contains an enzyme neuraminidase which is essential for the replication of the virus.
- Neuraminidase inhibitors prevent the release of new virions and their spread from cell to cell.

#### Neuraminidase inhibitors : Influenza Oseltamivir / Zanamavir

- These are effective against both types of influenza A and B.
- Do not interfere with immune response to influenza A vaccine.
- Can be used for both prophylaxis and acute treatment.



### **Anti-viral drugs** Neuraminidase inhibitors : Influenza Oseltamivir / Zanamavir

- Oseltamivir is orally administered.
- Zanamavir is given intranasal.
- Risk of bronchospasm with zanamavir

#### PHARMACOLOGY OF RIBAVIRIN

- Ribavirin is a guanosine analog.
- Inhibition of RNA polymerase

#### Antiviral spectrum : DNA and RNA viruses are susceptible, including influenza, parainfluenza viruses, RSV, Lassa virus

#### **Ribavirin : RSV**

- Distribution in all body tissues, except CNS
- Administration : Oral, IV, Inhalational in RSV.
- Anemia and jaundice are adverse effects
- Not advised in pregnancy.

#### Therapeutic uses Ribavirin *Ribavirin is the drug of choice for:*

- RSV bronchiolitis and pneumonia in hospitalized children (given by aerosol)
- Lassa fever

#### Ribavirin is an alternative drug for:

• Influenza, parainfluenza, measles virus infection in immunocompromised patients

Hepatic Viral infections :

- Interferons
- Lamivudine cytosine analog HBV
- Entecavir guanosine analog HBV – lamivudine resistance strains
- Ribavirin Hepatitis C (with interferons)

#### Interferons

- Interferons (IFNs) are natural proteins produced by the cells of the 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  $\alpha$  ,  $\beta$ ,  $\gamma$

### Interferons

- 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*
- $\gamma$  has less anti-viral activity compared to  $\alpha$  and  $\beta$  interferons

#### Mechanism of action of Interferons :

- Induction of the following enzymes:
- 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%</li>
- Administered Intralesionally, S.C, and I.V
- Distribution in all body tissues, except CNS and eye.
- Half lives: 1-4 hours



#### Adverse effects of Interferons

- Acute flu-like syndrome (fever, headache)
- Bone marrow suppression (granulocytopenia, thrombocytopenia)
- Neurotoxicity (confusion, seizures)
- Cardiotoxicity arrhythmia
- Impairment of fertility

#### **Therapeutic uses 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

Viru	Diseases	Drug(s) of choice	Alternative drugs
FLU A	Influenza	Amantadine	Rimantadine
RSV	Pneumonia, bronchiolitis	Ribavirin (aerosol)	
HSV	Genital herpes	Acyclovir	Foscarnet
	Keratitis Conjunctivitis	Trifluridine	Idoxuridine Vidarabine
	Encephalitis	Acyclovir	
	Neonatal HSV infection	Acyclovir	Vidarabine
1/18/12	Herpes infections in immuno- compromised host <sub>Dr.T</sub>	Acyclovir	Foscarnet

VZV	In normal host	No therapy	
	In immunocompro- mised host, or during pregnancy	Acyclovir	Foscarnet
CMV	Retinitis	Ganciclovir	Foscarnet
HIV	AIDS HIV antibody positive with CD4 count < 500/mm <sup>3</sup>	Zidovudine ± protease inhibitors	Didanosine, Stavudine
HBV HCV 11/18/12	Hepatitis B, C	Interferons	52

HAART - Highly active antiretroviral therapy

 Includes at least three medications

- "cocktails"

 These medications work in different ways to reduce the viral load



#### • <u>Reverse transcriptase inhibitors (RTIs)</u>

Block activity of the enzyme reverse transcriptase, preventing production of new viral DNA

#### <u>Reverse transcriptase inhibitors (RTIs)</u>

- Nucleoside RTIs (NRTIs)
- Nonnucleoside RTIs (NNRTIs)
- Nucleotide RTIs (NTRTIs)

#### • Examples

abacavir (Ziagen) didanosine (Videx) stavudine (Zerit)

delavirdine (Rescriptor) lamivudine (Epivir) tenofovir (Viread)

- <u>Protease inhibitors</u>
   <u>(PIs)</u>
- Inhibit the protease retroviral enzyme, preventing viral replication
- <u>Examples:</u>

amprenavir (Agenerase) indinavir (Crixivan) nelfinavir (Viracept) ritonavir (Norvir) saquinavir (Invirase)



- Fusion inhibitors
- Inhibit viral fusion,
   preventing viral
   replication
- Newest class of antiretroviral drugs
- Example: enfuvirtide (Fuzeon)



- Combinations of multiple antiretroviral medications are common
- Adverse effects vary with each drug and may be severe-monitor for doselimiting toxicities
- Monitor for signs of opportunistic diseases