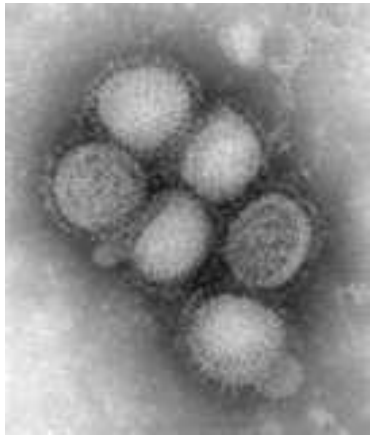
ANTI VIRAL AGENTS



What are anti-virals?

- An antimicrobial used specifically for treatment of viral infections

How do they act?

- Do not destroy the target pathogen. They inhibit the development.

Problems in producing anti viral agents

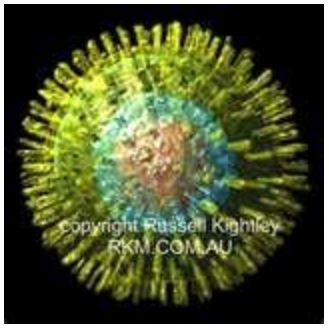
- Viruses use the host cell to replicate
- Viral variation

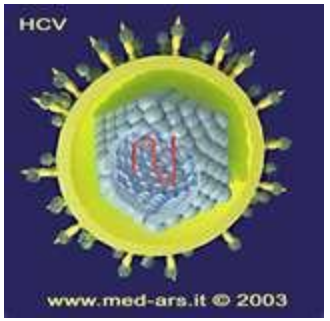
- Viruses → DNA
  → RNA

- Viruses – intracellular
  - metabolically inert
  - replication by incorporation into host DNA

Antiviral agents → Need highly selective toxicity

DNA	RNA
Herpes viruses Herpes simplex Varicella zoster Cytomegalovirus Epstein-barr virus **Hepatitis B virus** **Human papilloma virus** **Parvovirus** **Pox viruses** Variola virus Vaccinia virus Orf virus Molluscum contagiosum	Polio Coxsackie Entero Rhino Rota Measles Mumps Rubella Rabies **Hepatitis A, C, D, E** Influenza A, B, C RSV **Dengu virus** **Zika virus** **HIV** **Ebola** Hanta





- **Latent infection and reactivation** (herpes viruses)

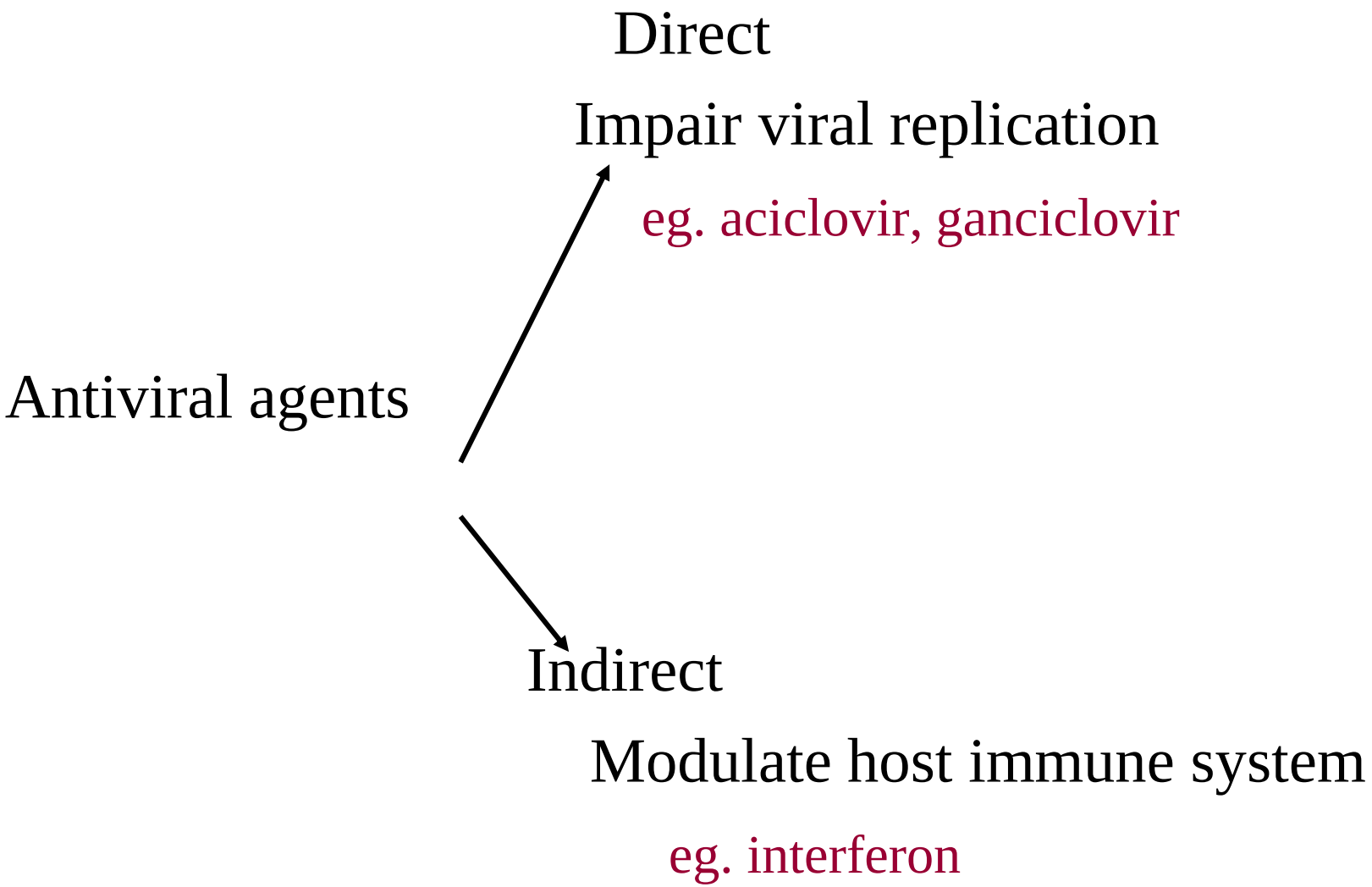
  Prophylactic drugs in immunocompromised

- Antivirals most effective during **active viral replication**

  Earlier the treatment → better the outcome

  (Symptoms: only after substantial multiplication)

- Viruses → Capable of developing **resistance**


Direct
Impair viral replication
eg. aciclovir, ganciclovir
Antiviral agents
Indirect
Modulate host immune system
eg. interferon

Infection		1st line Rx
Herpes simplex	Genital Herpes	**Oral aciclovir / valaciclovir**
	Herpes labialis	**Penciclovir cream**
	Herpes keratitis	**Aciclovir eye ointment**
	immunocompromised	**IV aciclovir**
	Herpes encephalitis	
	Disseminated Herpes	
	Neonatal herpes	

Infection		1st line Rx
Chickenpox 	immunocompetent with no complications	**oral aciclovir**
	immunocompromised	**IV aciclovir**
	with complications	
Herpes zoster 	immunocompetent with no complications	**Oral aciclovir**
	with ophthalmic involvement	
	immunocompromised	**Iv aciclovir**

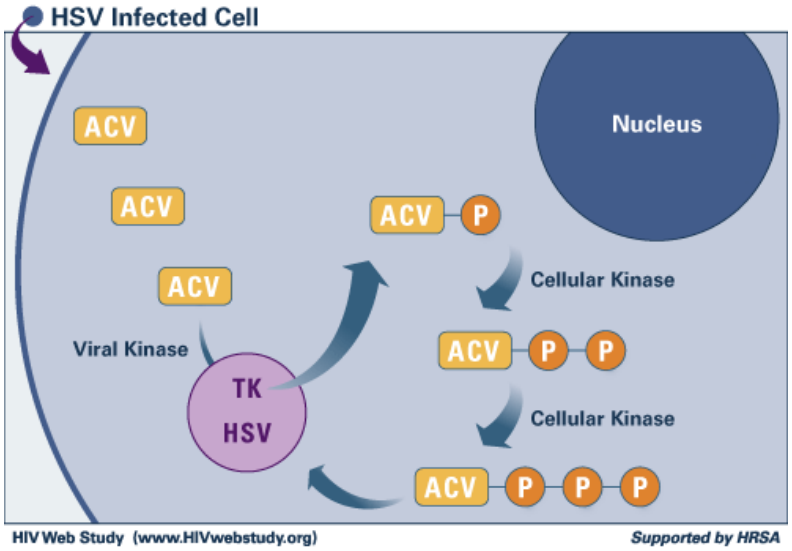
Infection	1st line Rx
Cytomegalovirus	**IV Ganciclovir**
Influenza A	**Oral Rimantadine / amantadine**
Novel Influenza A H1N1	**Oral Oseltamivir / Zanamavir**
Chronic hepatitis B	**sc Interferon alpha / oral lamivudine**
Chronic hepatitis C	**sc Interferon alpha + oral Ribavirin**
HIV	**HAART**

Aciclovir

Mechanism of action

A nucleoside analogue

Inhibits viral DNA synthesis



aciclovir → phosphorylated aciclovir

virus specific thymidine kinase

- compete with nucleosides
- incorporated into viral DNA irreversibly

↓

inhibition of viral DNA polymerase

Aciclovir…

Pharmacokinetics

- **GI absorption 20%**
  - Milder infections → oral
  - Severe infections → IV

- **CSF concentration = ½ plasma concentration**

  Important for dosing in viral encephalitis

- T 1/2 3hrs

  Dosing : **5 times/ day** when given orally

- Renal excretion

  Reduce dose in renal impairment

Aciclovir…

Clinical Uses

- Herpes simplex (HSV1 & HSV2)
  - Herpes labialis
  - stomatitis
  - keratitis, dendritic ulcer (in eye)
  - encephalitis
  - disseminated infection
  - genital herpes

- Varicella zoster (VZV)
  - chickenpox
  - shingles (herpes zoster)

Aciclovir…

HSV – oral aciclovir

200mg 5 times/ day x 5 days

- IV aciclovir 10mg/kg 8hrly

  x 7 days in mucocutaneous infection

  x 14 days in neonatal herpes

  x 14 – 21 days in encephalitis

half dose in renal failure

Aciclovir…

Varicella zoster

Chickenpox - immunocompromised IV
- complications IV
- neonates IV
– > 16 years oral

Shingles - immunocompromised IV
- ophthalmic division involvement oral
- >50 years oral
- moderate – severe pain oral

Oral aciclovir – 800mg 5 times / day (20mg/kg)

IV aciclovir – 10mg/kg

Best within first 48 – 72 hours

Aciclovir…

Adverse Effects

oral/iv - GI symptoms

- headache
- reversible nephropathy (with IV use)
- encephalopathy
- rashes

eye ointment – irritation

- punctate keratopathy

iv extravasation – local inflammation

Drugs similar to Aciclovir

- Penciclovir
- Famciclovir (prodrug of penciclovir)

  longer t ½

  given 8 hourly

- Valaciclovir – a pro drug of aciclovir

  - bioavailability higher than aciclovir (3 – 5 folds)

Ganciclovir

- Mechanism of action → similar to aciclovir
- Effective against HSV 1 & 2, VZV; also against CMV
- Limiting factor : **toxicity**
  Limited clinical uses; only for CMV
- Oral/ IV
  bioavailability very low (8-9%)
- T ½ 12hrs
- Excreted in urine unchanged

Ganciclovir…

Clinical uses

Cytomegalovirus infection

– treatment of life or sight threatening infection

- Prophylaxis in immunocompromised

Ganciclovir…

- Adverse effects

- bone marrow suppression
  usually (but not always) reversible
- renal impairment
- fever
- headache
- rash
- GI symptom
- confusion, seizures (encephalopathy)

- Contraindicated in pregnancy

Lamivudine

- A reverse transcriptase inhibitor and

  HBV DNA polymerase inhibitor

- **High bioavailability**

- Long t ½

Lamivudine…

Clinical uses

- Hepatitis B – 100mg daily po X 1 year

  Can be used in decompensated liver disease

- HIV/AIDS - in combination with other anti-retrovirals

Adverse effects - minimal

- Hepatic steatosis
- lactic acidosis
- peripheral neuropathy

} rare

Interferon

- Virus infection → stimulates interferon production
  Part of normal host immune response

- Interferon

- act on uninfected cells & protect them from viral invasion

- enhance immune response against infected cells

Interferon…

- 3 types; alpha, beta, gamma
- Interferon alpha

Hepatitis B, C, D

Hepatitis B – 5MU daily or 10 MU 3 times/wk
x 4 – 6 months

Hepatitis C – alpha interferon combined with ribavirin
- 3MU 3 times/week
x 6 – 12 months

Hepatitis D – 10MU 3 times/week x 12 months
Given subcutaneously 3 times per week

Interferon…

Interferon alpha…

Adverse Effects

- Common 80%

- Influenza like syndrome
- fatigue, headache
- depression

} respond to dose reduction

- convulsions
- BP changes
- arrhythmias
- BM suppression
- transient hepatitis

Interferon…

Interferon alpha…

Contraindications

- Decompensated liver disease
- Severe depression
- Thrombocytopenia/ Neutropenia

Pegylated interferon

- Polyethylene glycol chain attached to interferon

- Effectiveness more

  Duration of action longer

- Given once weekly in hepatitis B & C

Antiretroviral Agents

For treatment of HIV/AIDS

- Suppress viral replication

  Eradication not possible

- Prolongs life expectancy

- Limiting factors – Toxicity

  - Drug resistance

Antiretroviral Agents…

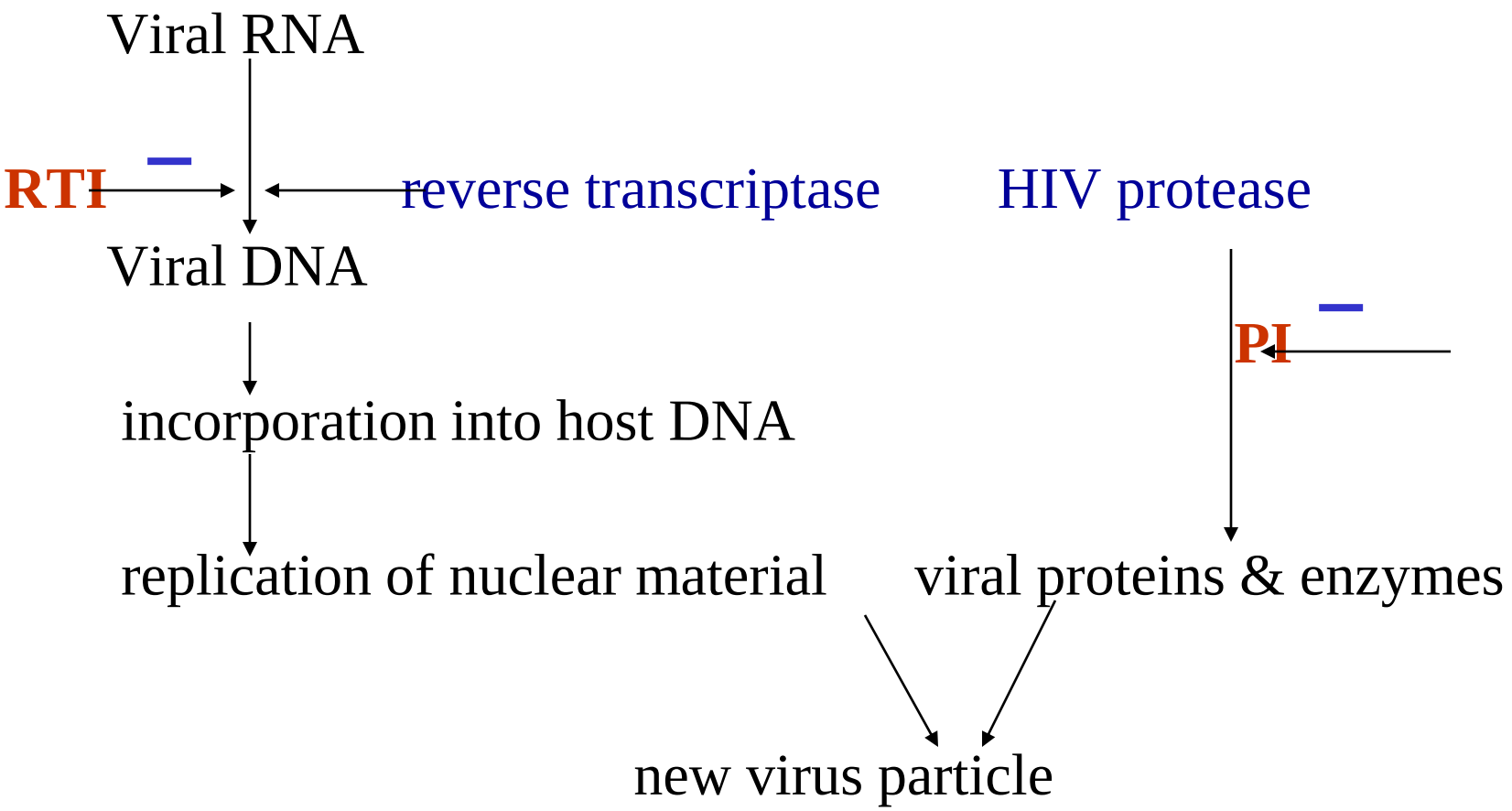
1. Reverse transcriptase inhibitors
   - nucleoside analogues (NA)
     eg. zidovudine, lamivudine, abacavir, didanosine
   - non-nucleoside reverse transcriptase inhibitors (NNRTI) eg. efavirenz, nevirapine
   - nucleotide analogues

2. Protease inhibitors
   eg. indinavir, nelfinavir, ritonavir, saquinavir

Antiretroviral Agents…

Mechanism of action

Virus particle ← nucleic acid (RNA) + protein



Antiretroviral Agents…

- Given orally as tablets

  2/3 drugs combined pills available

- Combination therapy – to prevent drug resistance

  At least 3 drugs

  2 NA + NNRTI / PI / abacavir as 3rd NA

HIV Post Exposure Prophylaxis (PEP)

- Duration of four weeks
- Their recommended regimen is emtricitabine + tenofovir + raltegravir

Antiretroviral Agents…

When to give?

- if symptomatic
- Asymptomatic with CD4 count < 200/microlitre
- Asymptomatic with CD4 200 – 350/microlitre + high viral load

(Not indicated when CD4 count >350 if asymptomatic)

- all pregnant mothers with HIV (from T2)
- Post-exposure prophylaxis (3 drugs x 4 weeks)

Antiretroviral Agents…

Adverse effects

- BM suppression
- osteoporosis, avascular necrosis
- mitochondrial toxicity → lactic acidosis
- Rashes, urticaria, fever
- Myalgia, arthralgia
- Headache, dizziness, insomnia,
- GI disturbances
- Hepatic damage
- Lipodystrophy syndrome (fat redistribution, insulin resistance, dyslipidaemia)
- Pancreatitis
- Psychiatric disturbances

Antiretroviral Agents…

Cautions

- Liver disease
- Renal impairment
- Pregnancy
- Elderly