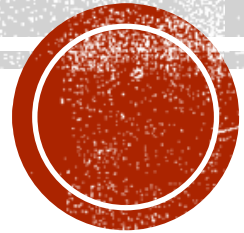
ANTIVIRAL DRUGS

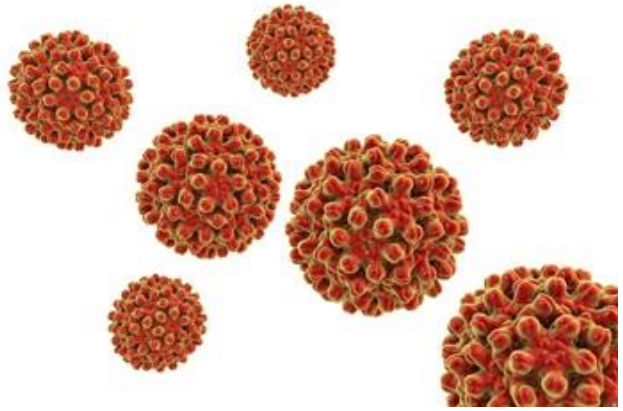
(INFLUENZA & HEPATITIS B&C)

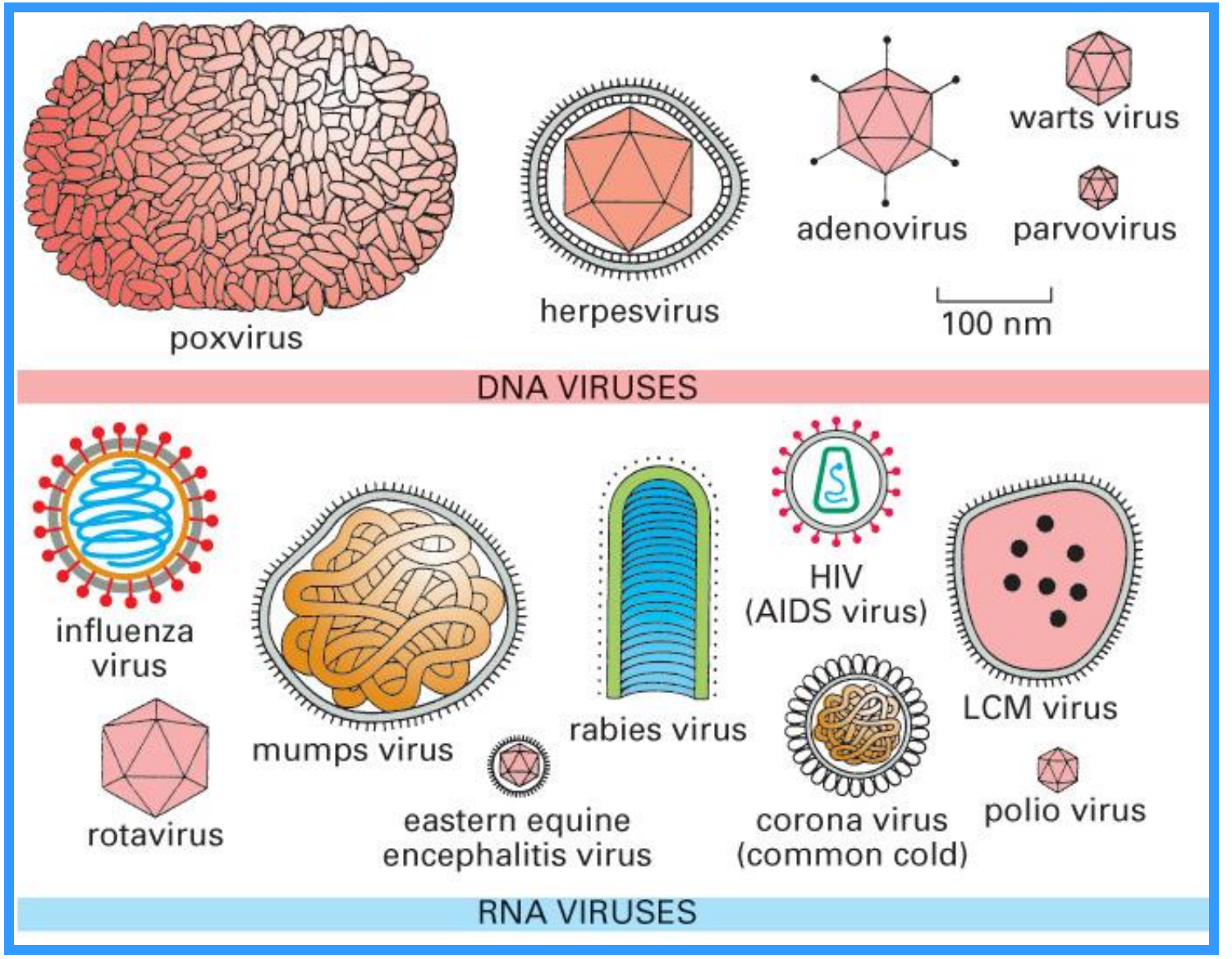


Dr. Asma inam

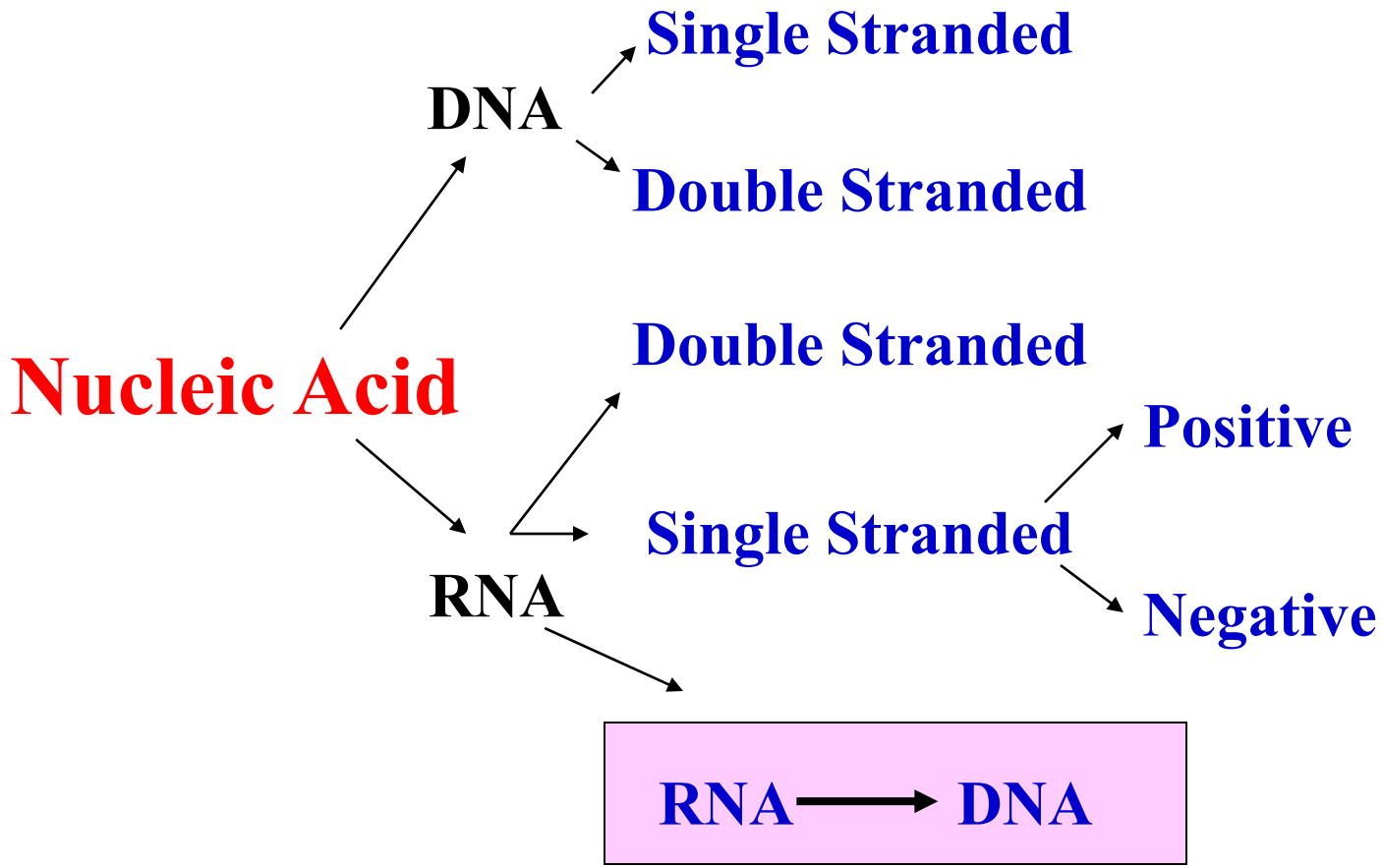
VIRUSES

- Are small infective agents consisting of nucleic acid (RNA or DNA) enclosed in a protein coat
- They are not proper cells and no metabolic machinery of their own
- They use the metabolic process of the host cell, which they enter and infect




poxvirus
herpesvirus
adenovirus
warts virus
parvovirus
100 nm
DNA VIRUSES
influenza virus
rotavirus
mumps virus
eastern equine encephalitis virus
rabies virus
HIV (AIDS virus)
corona virus (common cold)
LCM virus
polio virus
RNA VIRUSES

VIRAL GENOMES



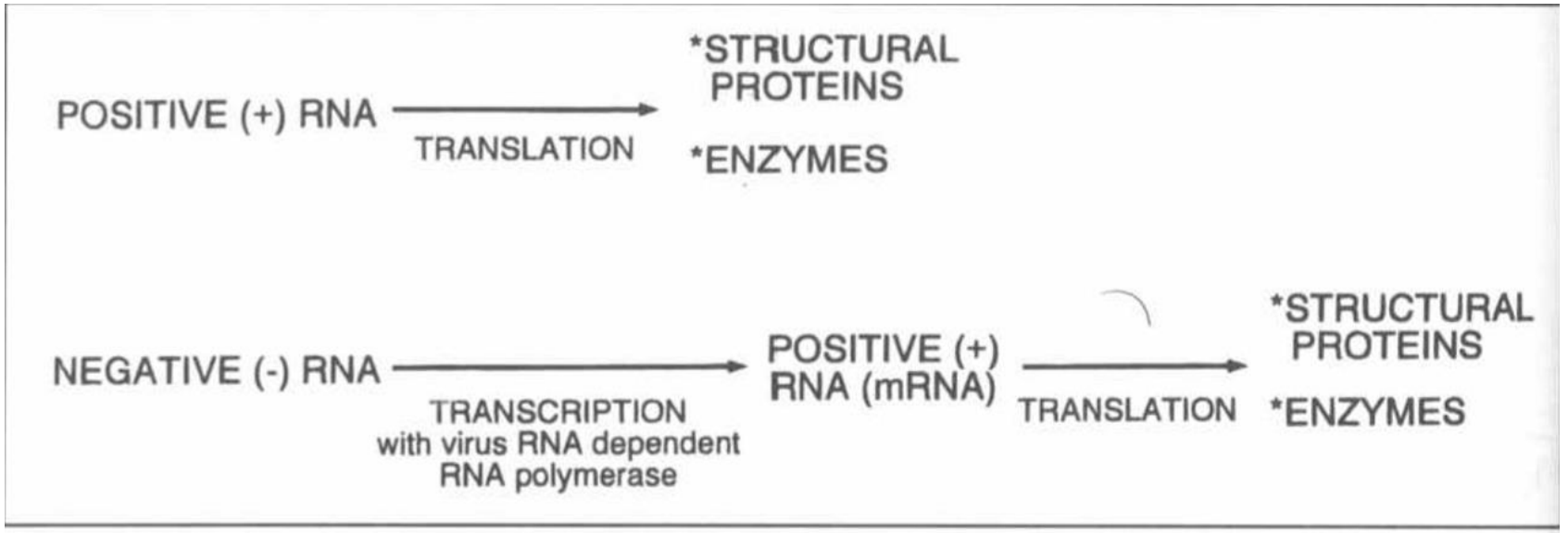
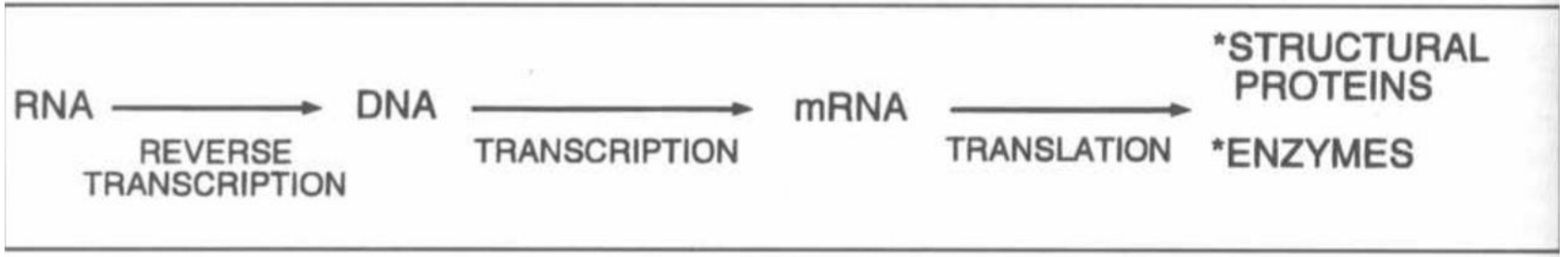
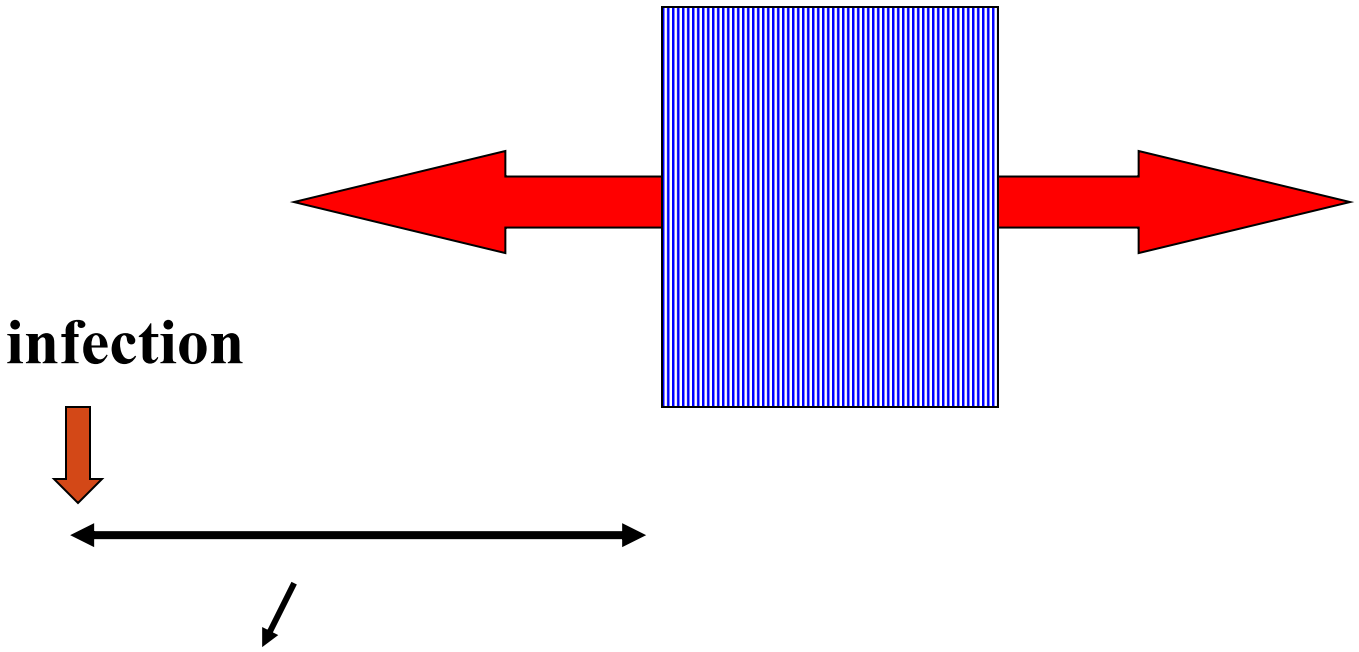

POSITIVE (+) RNA
TRANSLATION
*STRUCTURAL PROTEINS
*ENZYMES
NEGATIVE (-) RNA
TRANSCRIPTION with virus RNA dependent RNA polymerase
POSITIVE (+) RNA (mRNA)
TRANSLATION
*STRUCTURAL PROTEINS
*ENZYMES

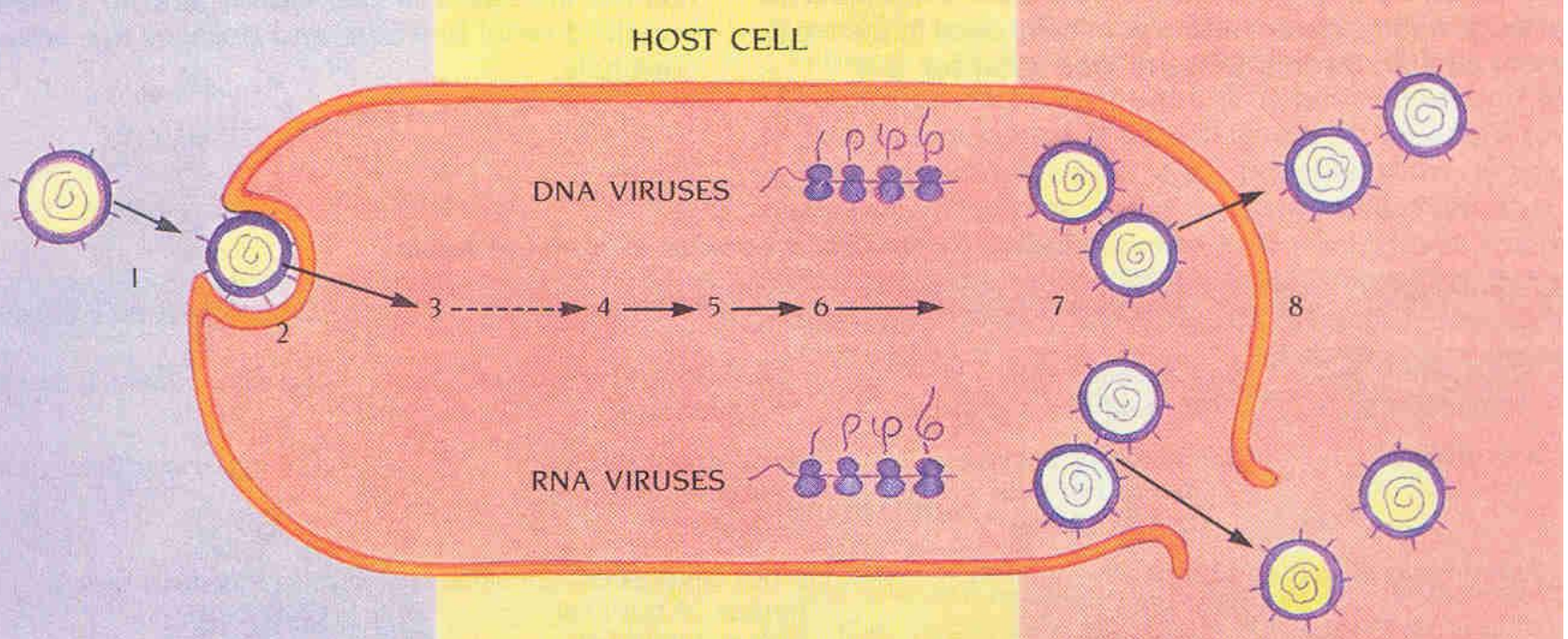
Figure 22-3


RNA
REVERSE TRANSCRIPTION
DNA
TRANSCRIPTION
mRNA
TRANSLATION
*STRUCTURAL PROTEINS
*ENZYMES

INCUBATION PERIOD



incubation period - time between infection and the appearance of clinical signs



A. INFECTION

1

Adsorption of virion to host cell plasma membrane receptors.

2

Entry of virion into host cell (akin to phagocytosis).

3

Uncoating of virion (*i.e.*, removal of protein capsid, exposure of viral nucleic acids to initiate replication).

B. REPLICATION

4

Viral DNA-dependent RNA polymerases (DNA viruses) and RNA-dependent RNA polymerases (RNA viruses) catalyse the synthesis of mRNAs for production of viral structural and non-structural proteins.

5

Viral genome may integrate into host chromosome.

6

Modification of viral proteins by glycosylation and cleavage.

C. RELEASE

7

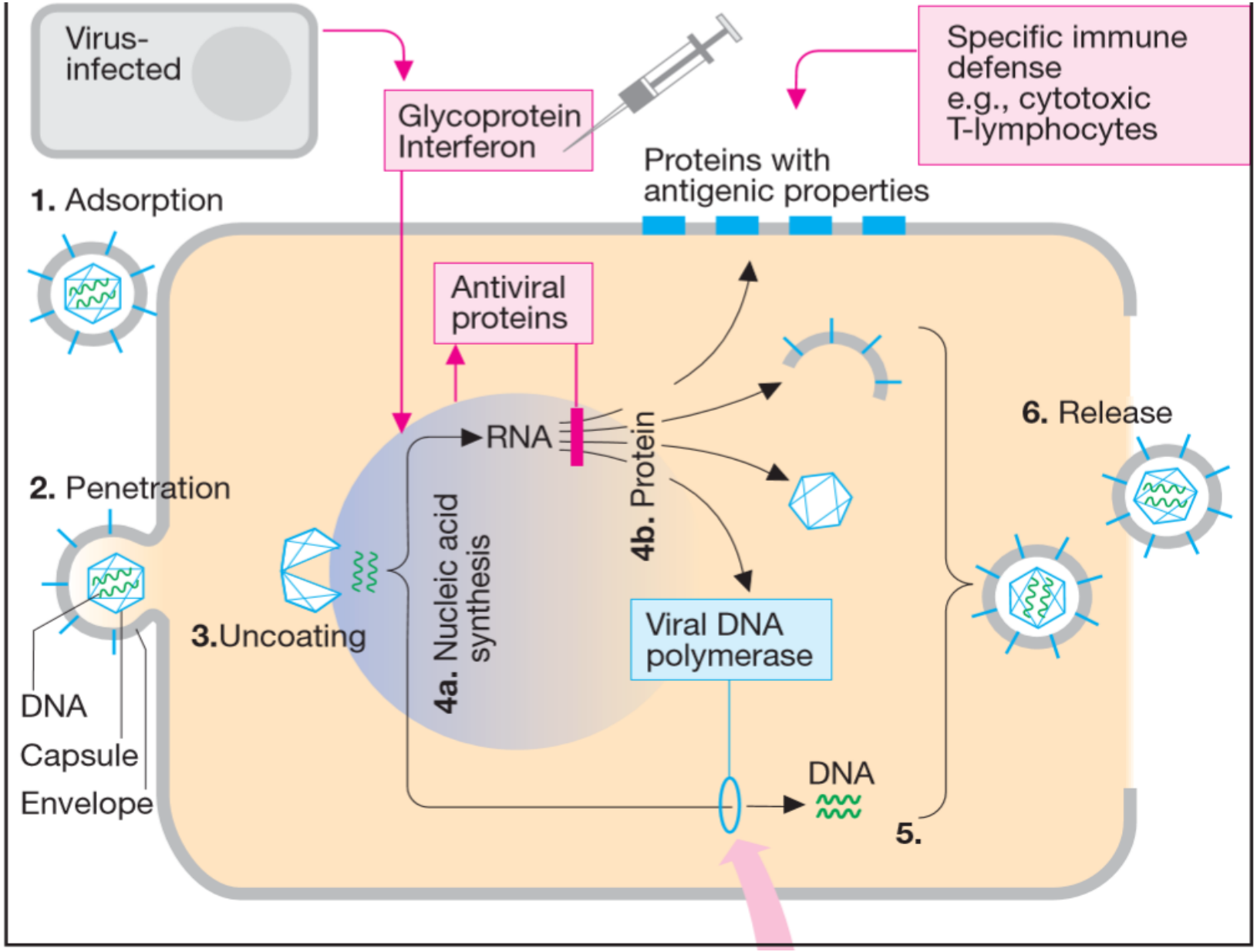
Assembly of virions.

8

Slow leakage from host cell (budding).

or

Cell rupture.


Virus-infected
Glycoprotein Interferon
Specific immune defense e.g., cytotoxic T-lymphocytes
Proteins with antigenic properties
1. Adsorption
Antiviral proteins
RNA
4b. Protein
6. Release
2. Penetration
3.Uncoating
4a. Nucleic acid synthesis
Viral DNA polymerase
DNA
Capsule
Envelope
DNA
5.

- Recent research has focused on the Identification of Agents with:
  - greater selectivity,
  - higher potency,
  - stability in vivo, and
  - reduced toxicity

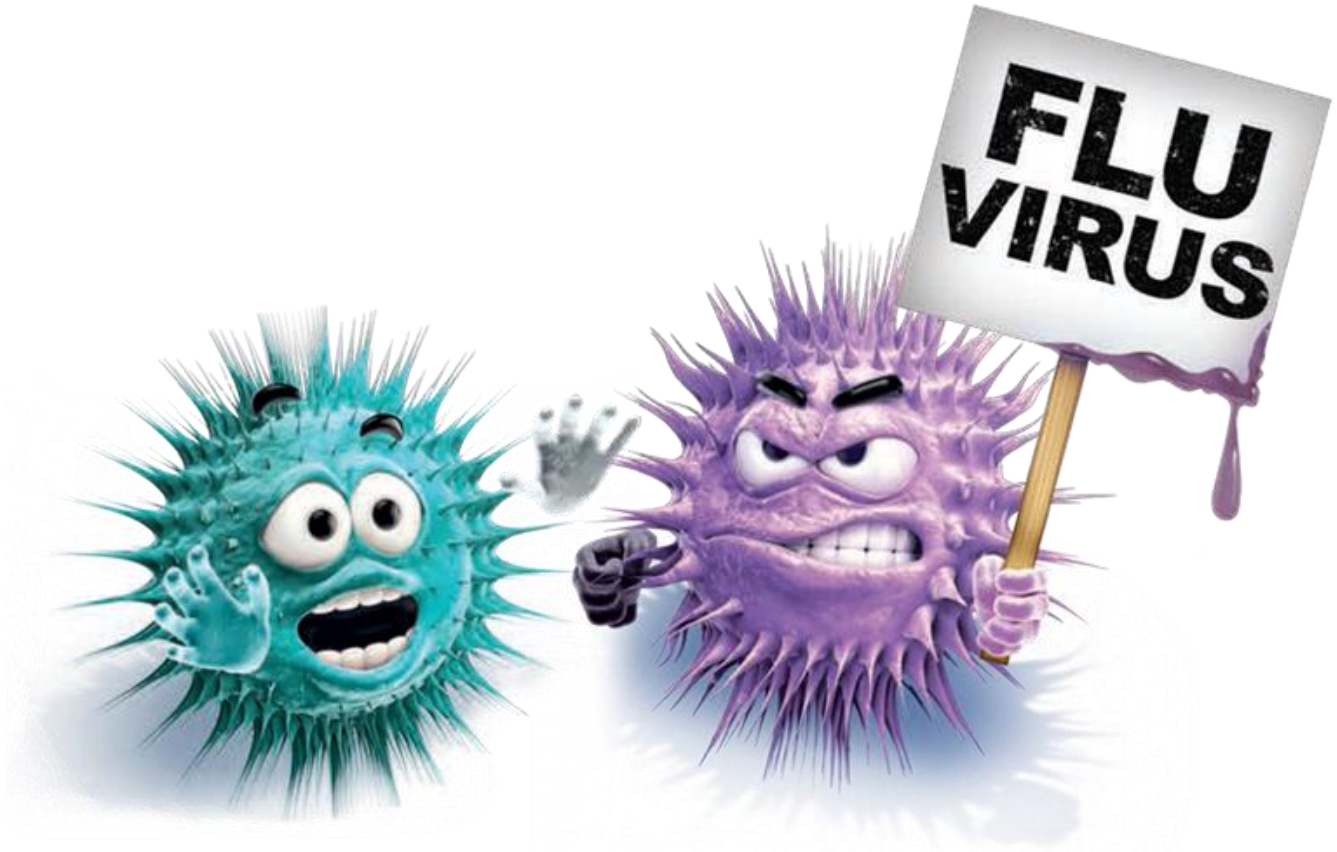
INFLUENZA A AND B

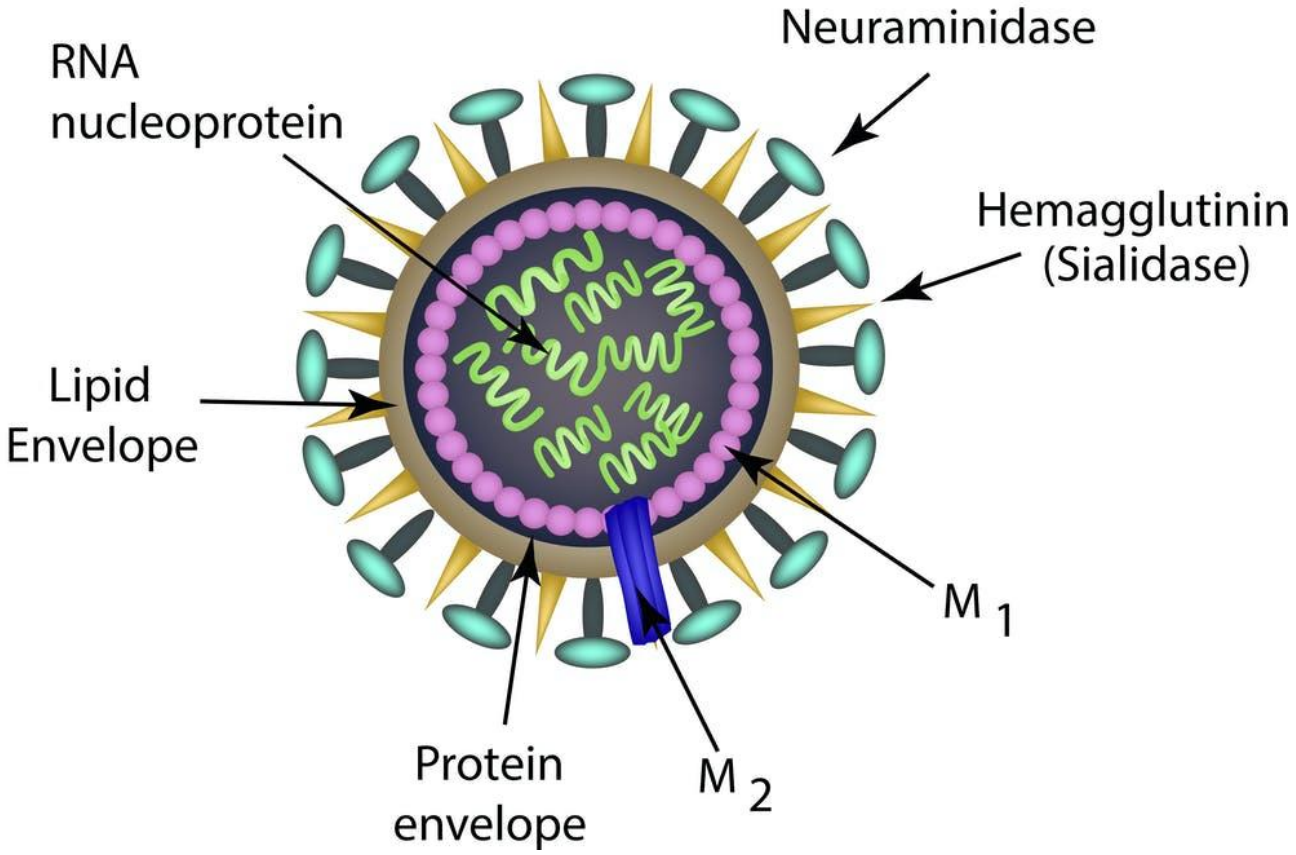
- amantadine rimantadine
- zanamivir oseltamivir

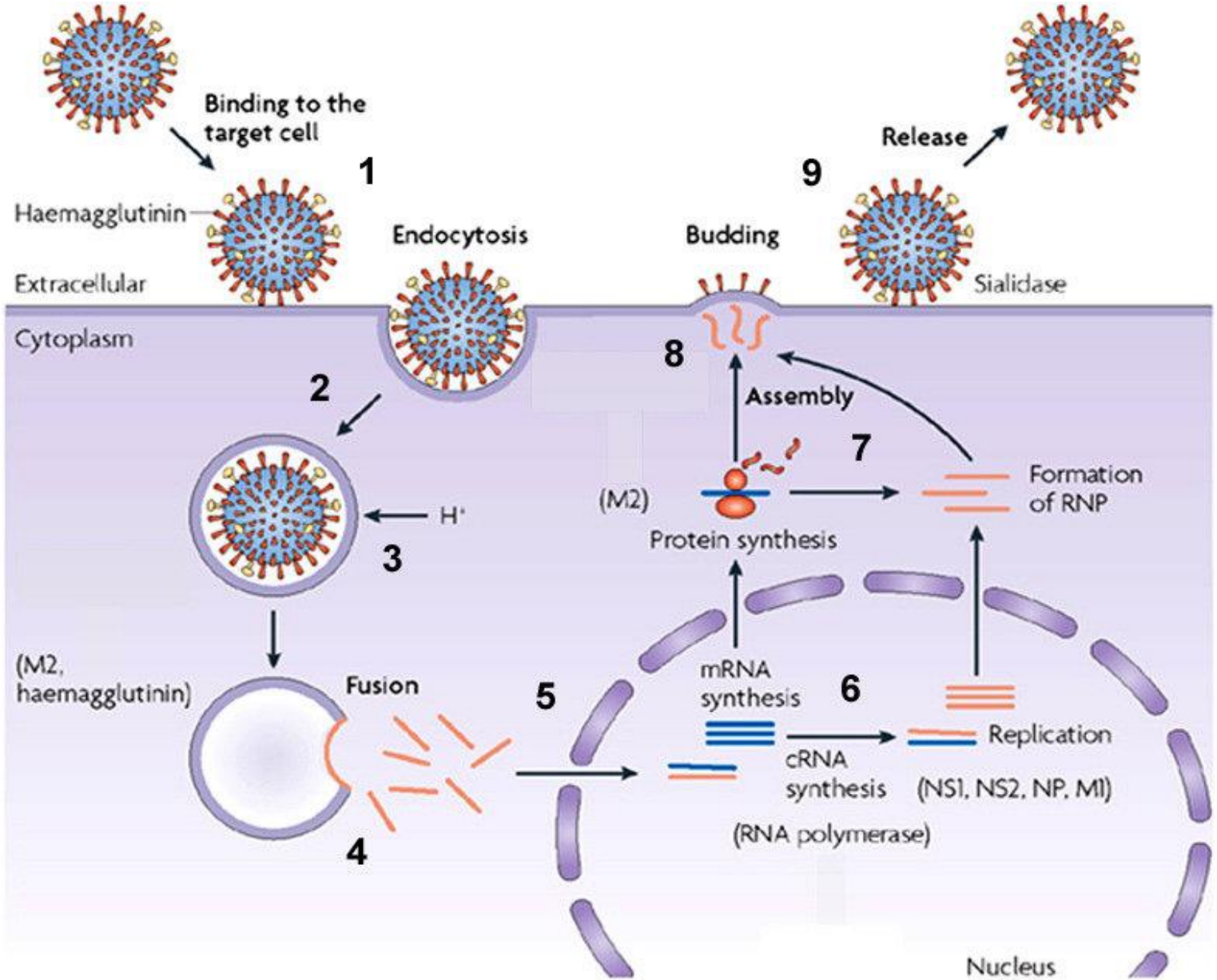
INFLUNZA H_5N_1 (BIRD FLUE):

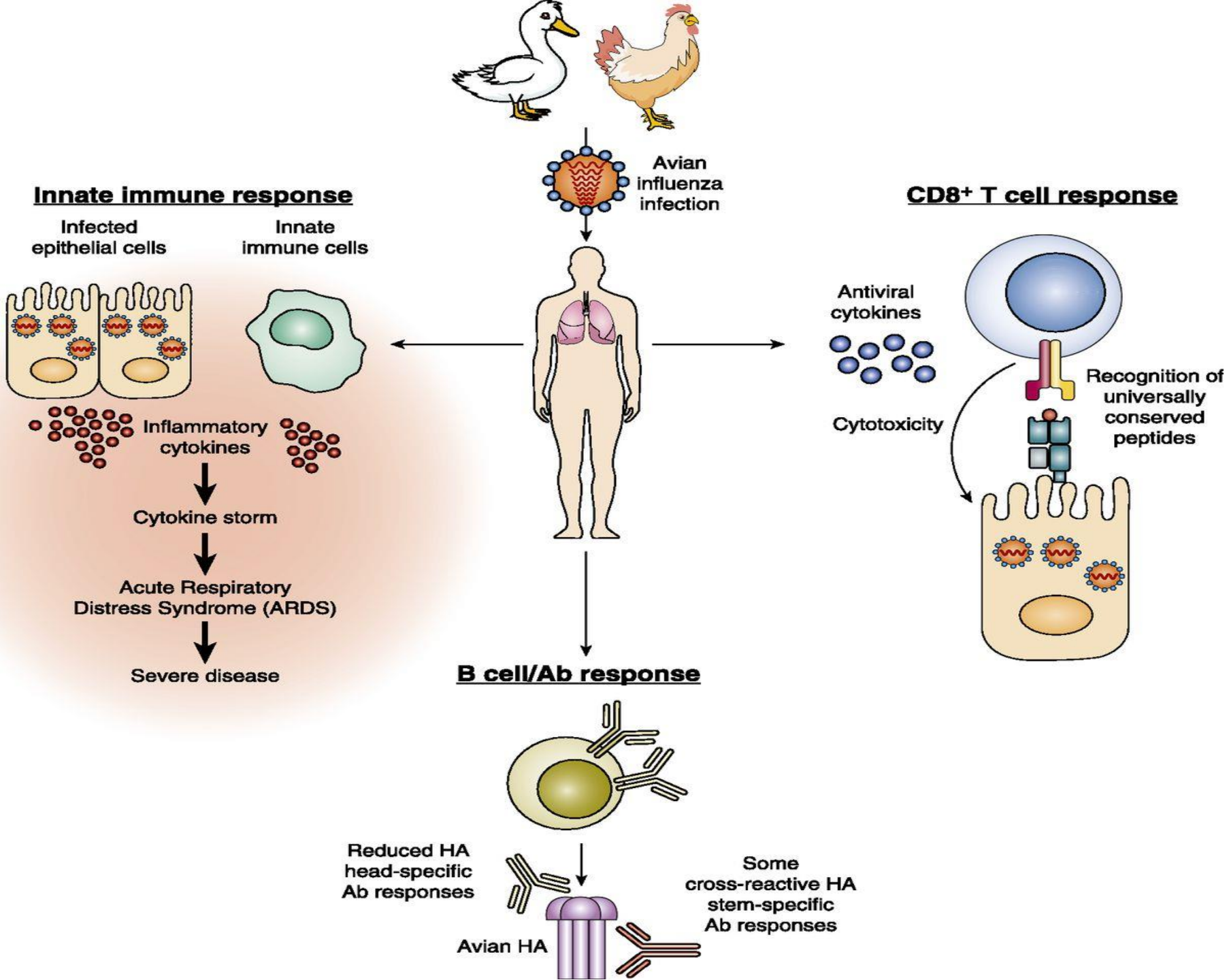
- tamiflue

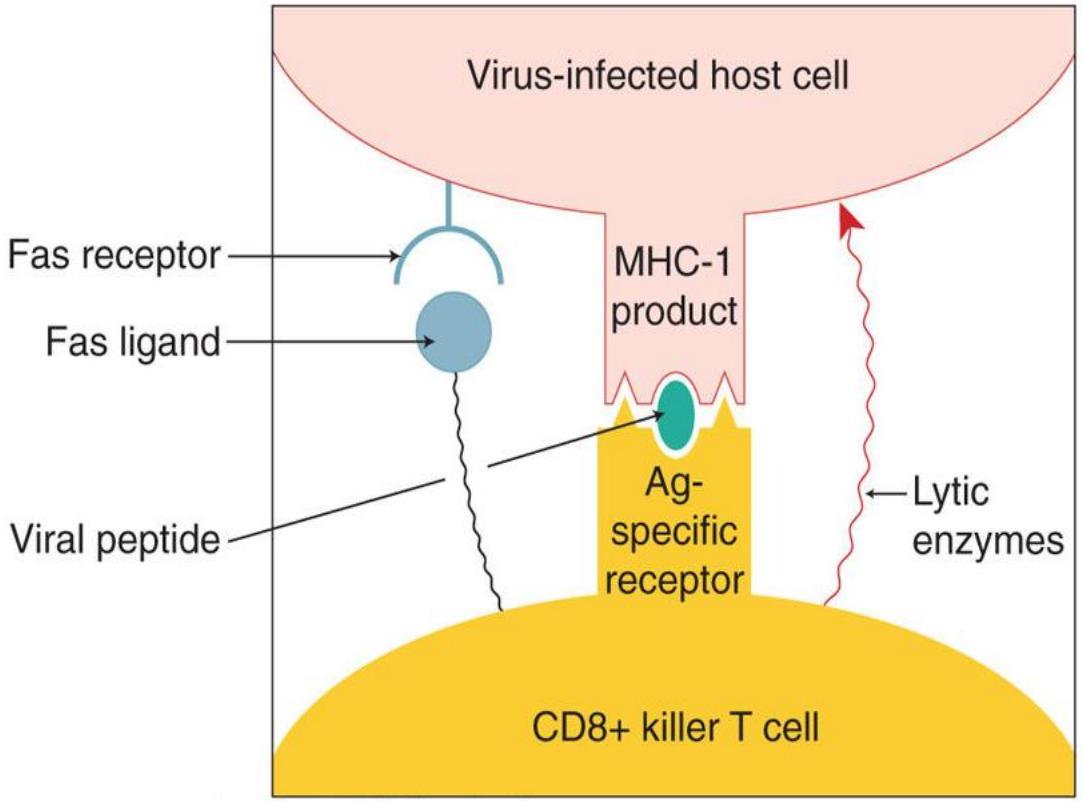
ANTI INFLUENZAE DRUGS




RNA
nucleoprotein
Neuraminidase
Hemagglutinin
(Sialidase)
Lipid
Envelope
M 1
Protein
envelope
M 2


Binding to the target cell
1
Haemagglutinin
Extracellular
Endocytosis
Budding
9
Release
Sialidase
Cytoplasm
8
2
Assembly
7
(M2)
Formation of RNP
H+
3
Protein synthesis
(M2, haemagglutinin)
Fusion
5
mRNA synthesis
6
Replication
cRNA synthesis
(NS1, NS2, NP, M1)
(RNA polymerase)
4
Nucleus


Avian influenza infection
Innate immune response
Infected epithelial cells
Innate immune cells
Inflammatory cytokines
Cytokine storm
Acute Respiratory Distress Syndrome (ARDS)
Severe disease
CD8+ T cell response
Antiviral cytokines
Cytotoxicity
Recognition of universally conserved peptides
B cell/Ab response
Reduced HA head-specific Ab responses
Some cross-reactive HA stem-specific Ab responses
Avian HA


Virus-infected host cell
Fas receptor
Fas ligand
MHC-1 product
Viral peptide
Ag-specific receptor
Lytic enzymes
CD8+ killer T cell

DRUG TREATMENT OF INFLUENZA A AND B

Immunization is preferred approach

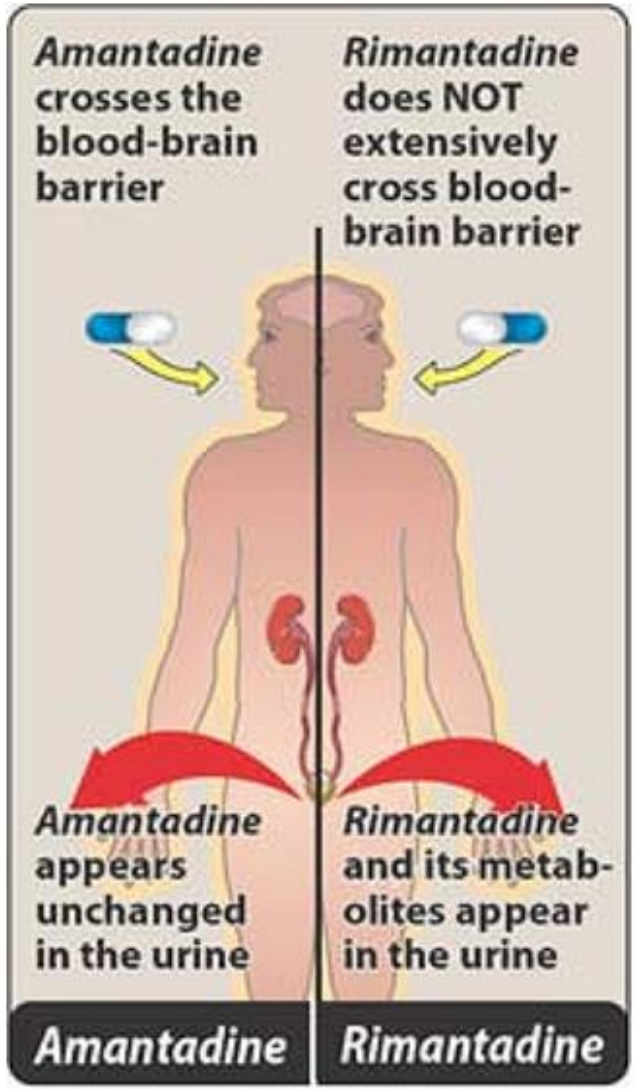
- amantadine , rimantadine (viral uncoating)
- zanamivir , oseltamivir (neuraminidase inhibitors)

INFLUNZA H_5N_1 (BIRD FLUE):

- tamiflue

AMANTADINE

- **Pharmacokinetics**
  - Given orally well absorbed from the gut
  - Reaches high levels in secretions
  - It also crosses the BBB (Ramintidine doesn’t)
  - t½ is 3 hrs
  - It is eliminated almost unchanged in urine


Amantadine crosses the blood-brain barrier
Rimantadine does NOT extensively cross blood-brain barrier
Amantadine appears unchanged in the urine
Rimantadine and its metab-olites appear in the urine
Amantadine
Rimantadine

AMANTADINE

Mechanism of Action:-

- A viral membrane protein M2 functions as an ion channel at the Time of entry into the cell
- Amantadine specifically blocks this ion channel
- Entry of virions from host cells

CLINICAL USES

1.For prophylaxis during influenza A virus

(Good alternative to vaccine for)

- Elderly
  - Immunocompromized
  - Allergic
  - Where causative strain not the vaccine
  - strain
  - Supplement to vaccine

2.Parkinson's disease

It potentiates the dopaminergic function

ADVERSE EFFECTS & CONTRAINDICATIONS

Unwanted effects are relatively infrequent occurring in 5-10%of patients

1) Dizziness, insomnia & slurred speech
2) Teratogenic

Contraindications are

Patients with history of seizures

Pregnancy

ZANAMIVIR & OSELTAMIVIR:

M.O.A

Inhibit neuraminidases of influenza A & B that prevent clumping of virions.

Oseltamivir is orally active prodrug.

CLINICAL USES:

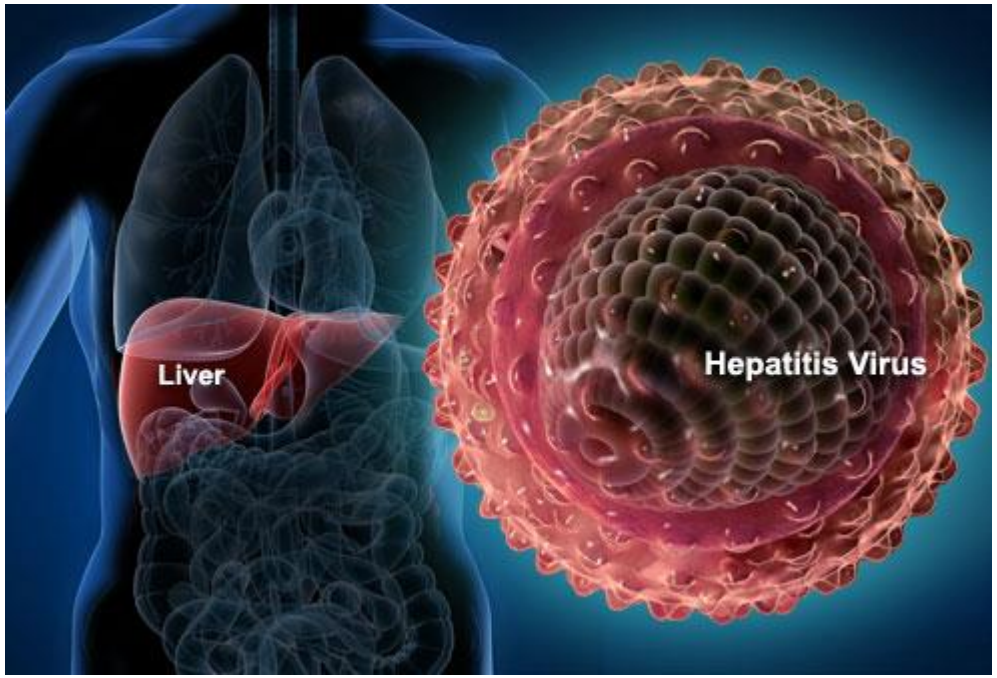
Prophylaxis mainly, also decreases duration symptoms

both type A&B

ADVERSE EFFECTS:

GI upset, nasal and throat irritation(Zanamivir)

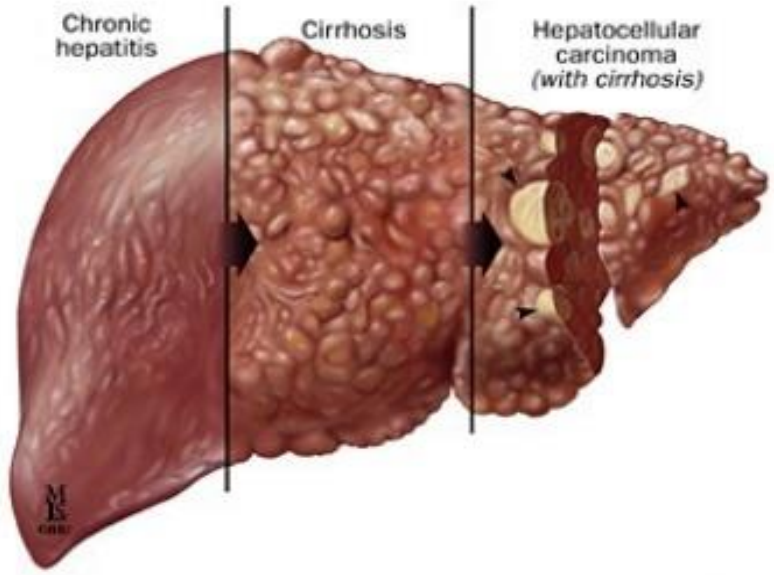
TREATMENT OF HEPATITIS B & C



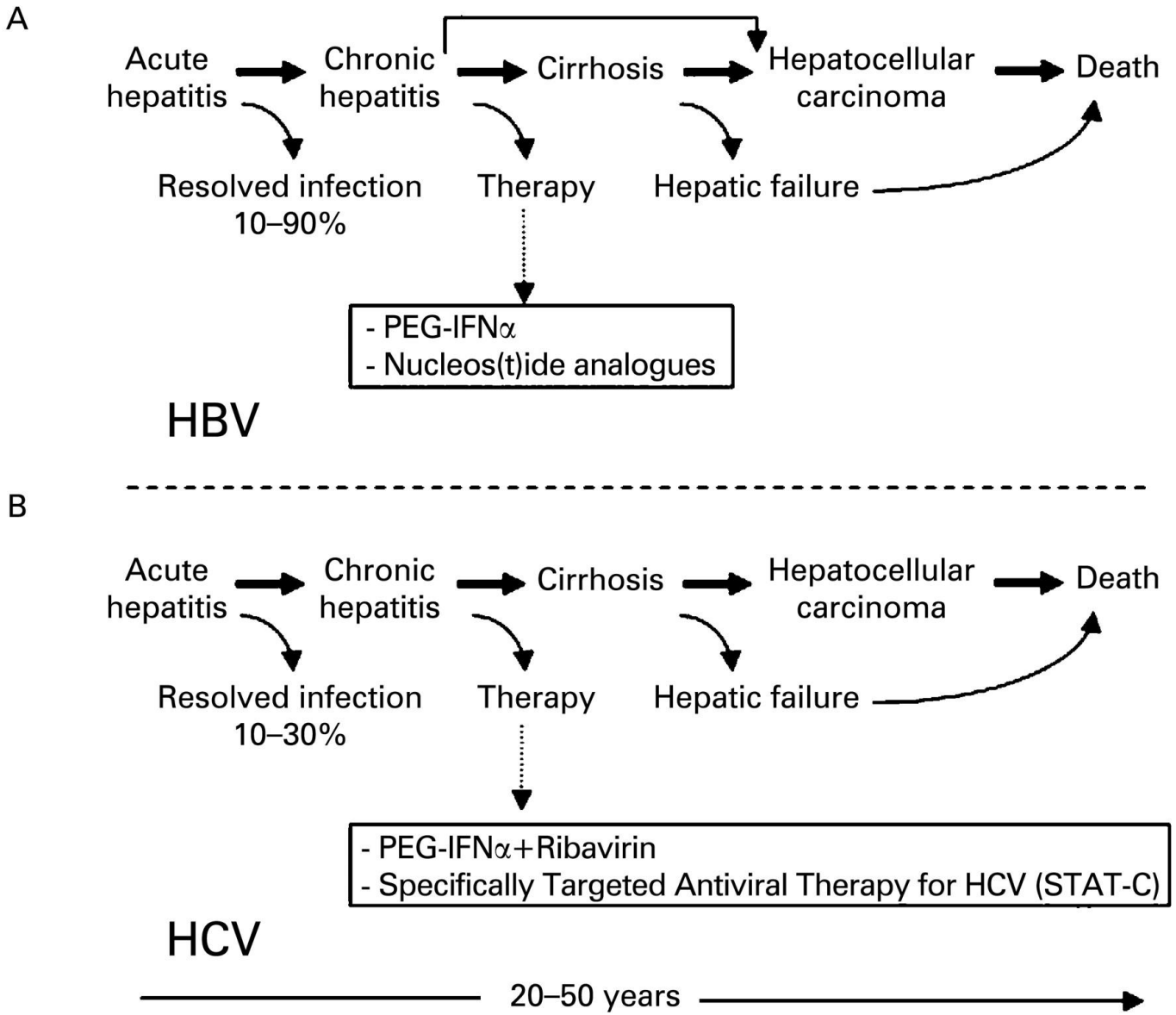
Hepatitis

- Hepatitis is a general term referring to inflammation of the liver

- Causes:
  - Infectious
    - Viral
    - Bacterial
    - Fungal
    - Parasitic
  - Non infectious
    - Alcohol
    - Drugs
    - Autoimmune
    - Metabolic diseases



Characteristic	Hepatitis A Virus	Hepatitis B Virus	Hepatitis C Virus
Type of virus	Picornavirus (RNA)	Hepadnavirus (DNA)	Flavivirus (RNA)
Mode of transmission	Fecal–oral (in some cases, parenteral)	Parenteral	Parenteral
Route of transmission	Person-to-person contact Sexual Food	Sexual Injection-drug use Perinatal (common, if mother is positive for hepatitis B early antigen)	Injection-drug use Blood products (before 1990) Sexual? Perinatal (infrequent)
Frequency of acute icteric disease	Common in adults Infrequent in children	Common in adults Infrequent in children	Uncommon
Frequency of evolution to chronic infection	Never	Infrequent in adults (<10%) Common in young children and infants	Frequent (>70%)
Estimated no. of acute infections/yr in the United States	179,000	185,000	38,000
Estimated no. of chronically infected persons in the United States	—	1,250,000	2,700,000
Estimated no. of chronically infected persons in the world	—	350,000,000	170,000,000
Treatment	None	Interferon alfa Lamivudine	Interferon alfa in combination with ribavirin
Prophylaxis	Recombinant vaccine Immune globulin (post-exposure)	Recombinant vaccine Hepatitis B immune globulin (postexposure)	None


A
Acute hepatitis
Chronic hepatitis
Cirrhosis
Hepatocellular carcinoma
Death
Resolved infection 10–90%
Therapy
Hepatic failure
- PEG-IFNα
- Nucleos(t)ide analogues
HBV
B
Acute hepatitis
Chronic hepatitis
Cirrhosis
Hepatocellular carcinoma
Death
Resolved infection 10–30%
Therapy
Hepatic failure
- PEG-IFNα+Ribavirin
- Specifically Targeted Antiviral Therapy for HCV (STAT-C)
HCV
20–50 years

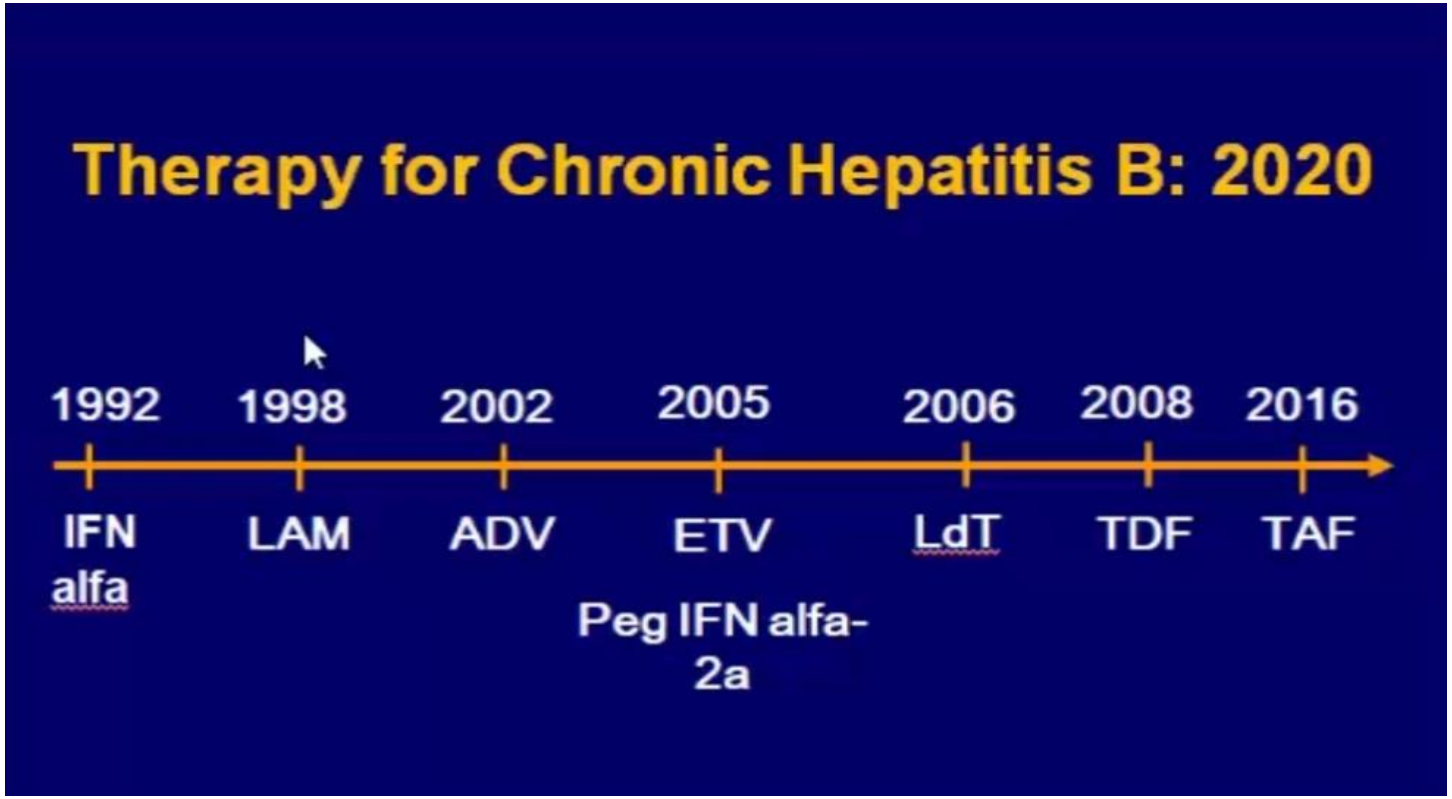
ANTI HEPATITIS DRUGS

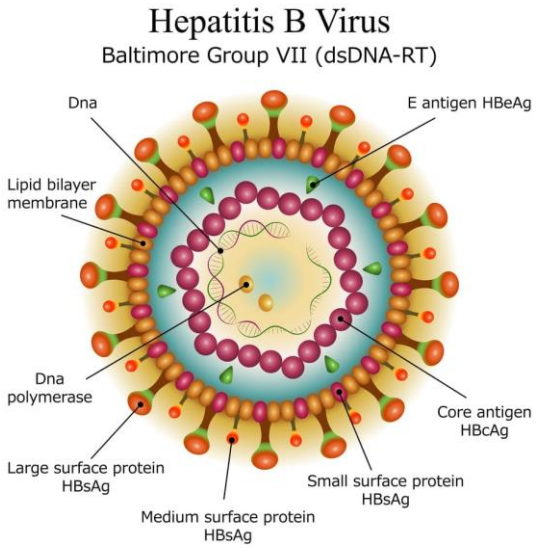
Antiviral therapy

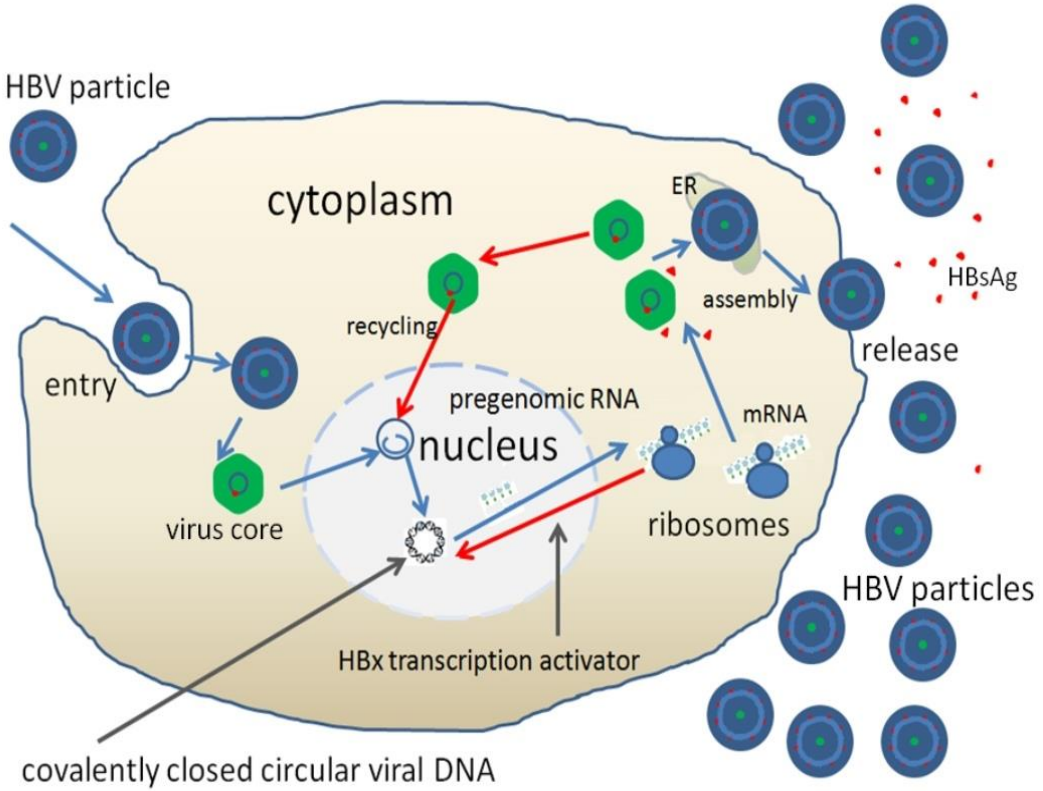
- Suppress viral DNA
- Reduce inflammation
- Reverse fibrosis
- Prevent decompensation
- Reduce the risk of HCC

ANTIVIRALS FOR HBV

- Interferon alpha-2b
- lamivudine, telbivudine
- adefovir, tenofovir, entecavir


Therapy for Chronic Hepatitis B: 2020
1992
1998
2002
2005
2006
2008
2016
IFN alfa
LAM
ADV
ETV
LdT
TDF
TAF
Peg IFN alfa-2a


Hepatitis B Virus
Baltimore Group VII (dsDNA-RT)
Dna
E antigen HBeAg
Lipid bilayer membrane
Dna polymerase
Core antigen HBcAg
Large surface protein HBsAg
Small surface protein HBsAg
Medium surface protein HBsAg


HBV particle
cytoplasm
ER
recycling
assembly
HBsAg
release
entry
pregenomic RNA
mRNA
nucleus
virus core
ribosomes
HBV particles
HBx transcription activator
covalently closed circular viral DNA

LAMIVUDINE

Pharmacokinetics:

oral 80% available, excreted unchanged

I/C Half life… longer

Clinical Use:

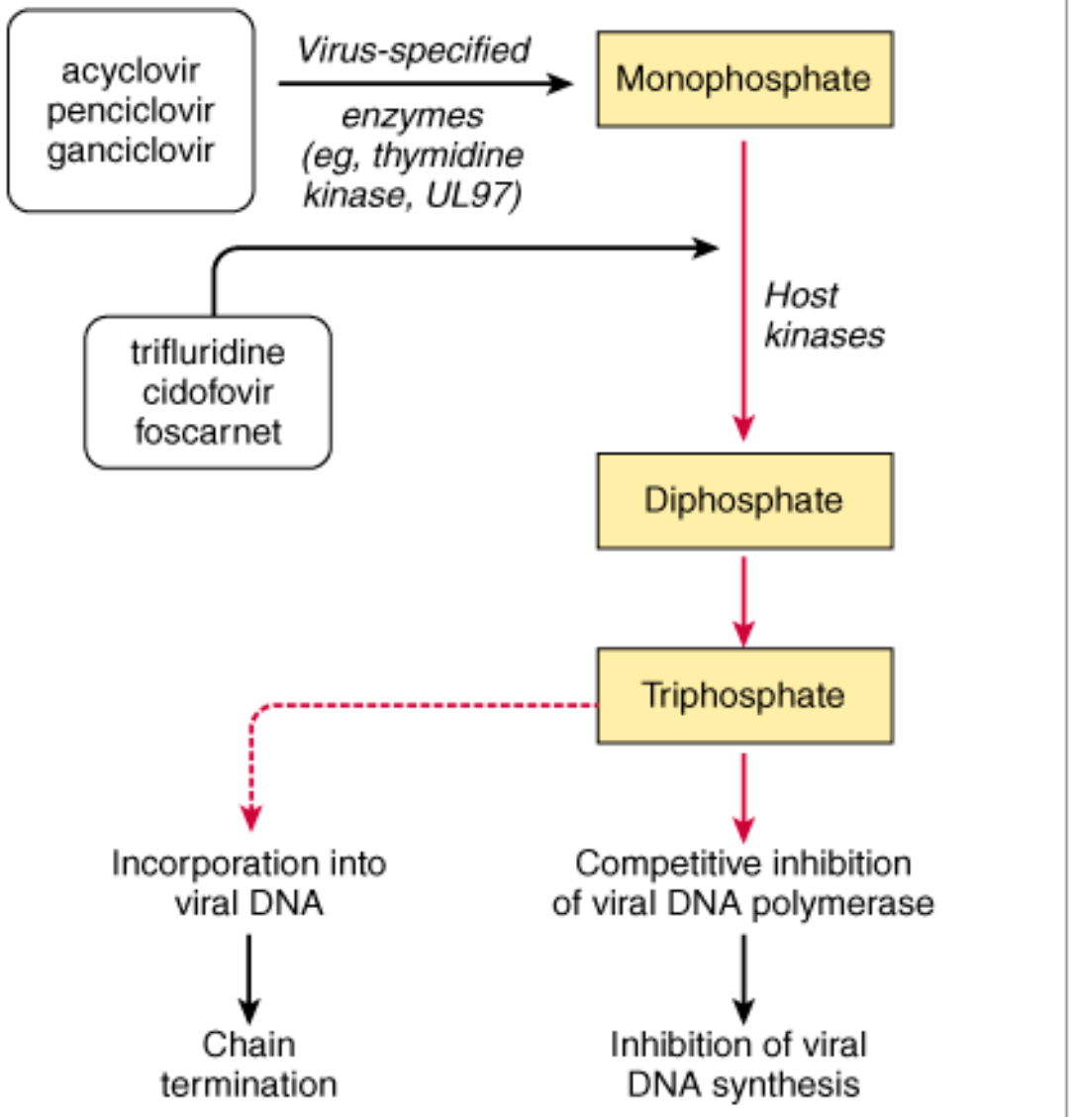
HBV, decrease HBV DNA level by 97% in 2 weeks.

Replication recur in 80% after discontinuation.

MECHANISM OF ACTION

- Must be activated to triphosphate form
- Inhibits HBV DNA polymerase
- Inhibits HIV reverse transcriptase

Figure 49–3


acyclovir
penciclovir
ganciclovir
Virus-specified
enzymes
(eg, thymidine
kinase, UL97)
Monophosphate
trifluridine
cidofovir
foscarnet
Host
kinases
Diphosphate
Triphosphate
Incorporation into
viral DNA
Chain
termination
Competitive inhibition
of viral DNA polymerase
Inhibition of viral
DNA synthesis

LAMIVUDINE

- 20% seroconversion, (HBAg negative), decrease liver fibrosis; ALT level decreases
- Lamivudine resistant.. IFN/ adefovir

Adverse Effects:

headache, dizziness

ADEFOVIR

- Lamivudine resistant
- MOA same
- Nephrotoxic
- Lactic acidosis
- Hepatomegaly

- Tenofovir..antiretroviral drug
- Lamivudine n entecavir resistant

IMMUNOMODULATORS

Interferon

These are a family of inducible proteins synthesised by the mammalian cells and now produced by recombinant DNA technology

There are at least three types α,β,γ constituting a family of hormones involved in cell growth, regulation & modulation of immune reactions

INTERFERON

Pharmacokinetics

- Given I/V, t½ 2-4 hours
- With I.M injection peak plasma concentration in 5-8 hours
- Do not cross the BBB
- Pegylated IFN?

Mechanism of Action:

- Produce cellular enzymes that inhibit the translation of viral mRNA into viral proteins
- Activate host cell ribonucleases degrades mRNA (receptor JAK/STAT)
- Increase NK cells that destroy infected liver cells.

A/E

- Flu like symptoms
- Bone marrow suppression
- Neurotoxicity
- Autoimmune disorder (thyroid)
- Arrhythmias
- Hearing loss, alopecia

CLINICAL USES

IFN α-2a is used for treatment of

- Hepatitis B infection
- AIDs related Kaposi sarcoma

IFN α-2b is used for treatment of

- Hepatitis C

Hairy cell leukemia

Interferons can prevent

- Activation of herpes simplex after trigeminal root section
- Spread of herpes –zooster in cancer patients

DDI

- Theophylline
- Zidovudine (bone marrow suppression)

Advantages of nucleoside/nucleotide analogs (NA) therapy of hepatitis over interferons (IFN)

- fewer adverse effects
- one-pill-a-day oral administration.

Advantages of IFN over NAs

- absence of resistance
- achievement of higher rates of viral agglutinin reduction.

Disadvantages of IFN

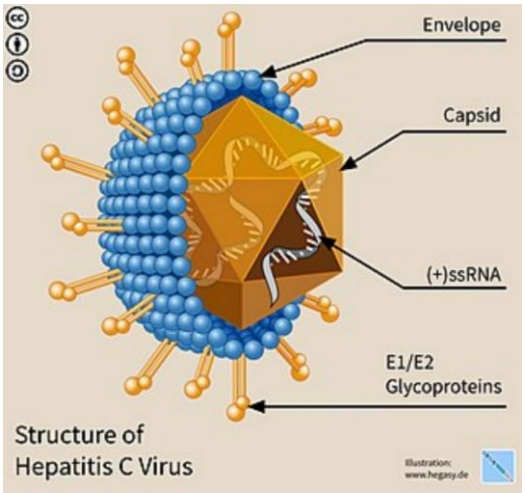
- less than 50% of persons treated will respond
- high cost
- administration by injection
- common adverse effects, which preclude its use in many persons and its contraindications

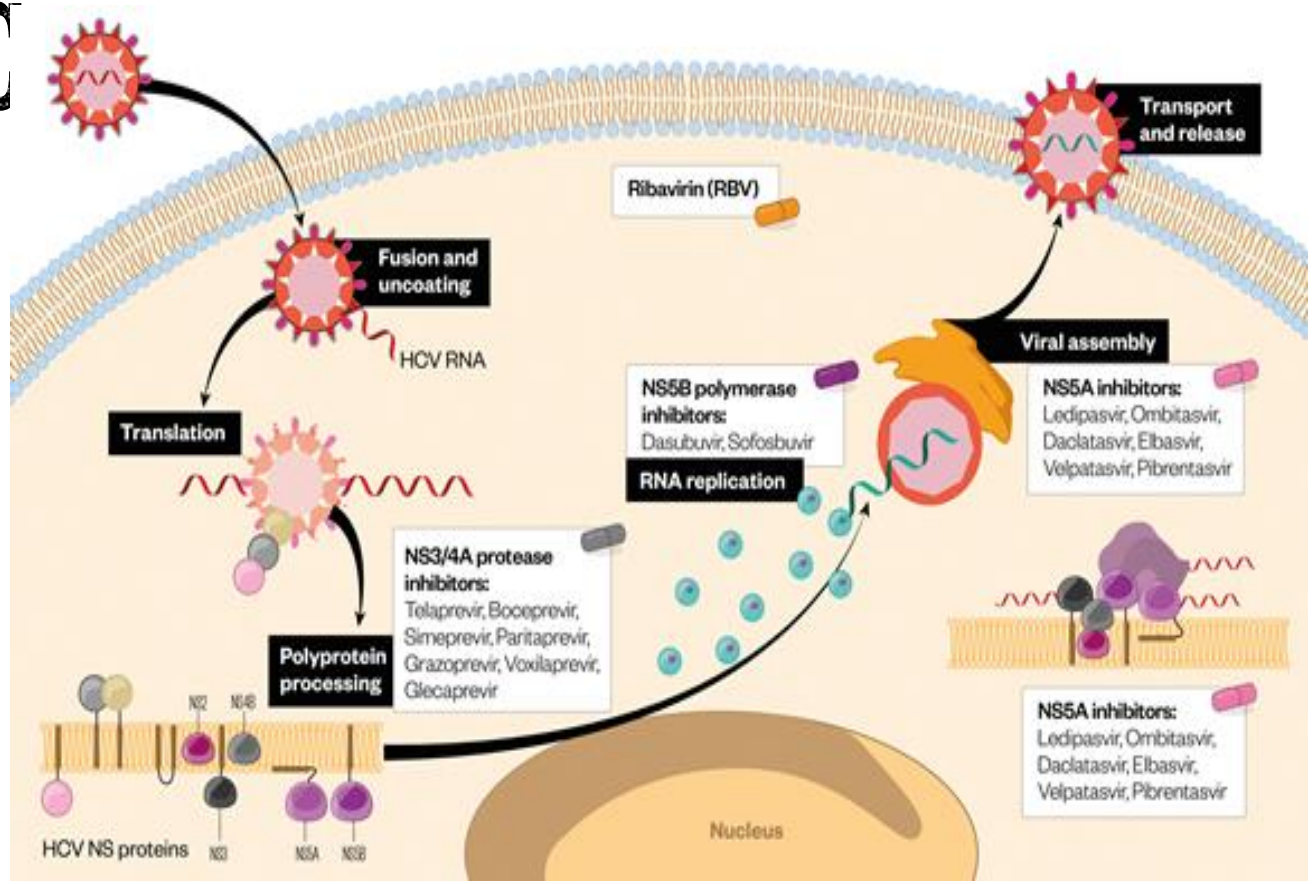
TABLE 49–6 Drugs used to treat chronic hepatitis B virus infection.

Agent	Recommended Adult Dosage	Potential Adverse Effects
Nucleoside/nucleotide analogs		
Entecavir[1]	500 or 1000 mg qd orally	Headache, fatigue, upper abdominal pain; lactic acidosis
Tenofovir alafenamide fumarate	25 mg qd orally	Nausea, abdominal pain, diarrhea, dizziness, fatigue, nephropathy, lactic acidosis
Tenofovir disoproxil[1]	300 mg qd orally	Nausea, abdominal pain, diarrhea, dizziness, fatigue, nephropathy, lactic acidosis
Adefovir dipivoxil[1]	10 mg qd orally	Renal dysfunction, lactic acidosis
Lamivudine[1]	100 mg qd orally	Headache, nausea, diarrhea, dizziness, myalgia, and malaise, lactic acidosis
Telbivudine[1]	600 mg qd orally	Fatigue, headache, cough, nausea, diarrhea, myopathy, peripheral neuropathy, lactic acidosis
Interferon alfa-2b	5 million IU/d or 10 million IU three times weekly subcutaneously or intramuscularly	Flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders
Pegylated interferon alfa-2a[1]	180 mcg once weekly subcutaneously	Flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders

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

HEPATITIS C


Envelope
Capsid
(+)ssRNA
E1/E2
Glycoproteins
Structure of
Hepatitis C Virus


Transport and release
Ribavirin (RBV)
Fusion and uncoating
HCV RNA
Viral assembly
NS5B polymerase inhibitors:
Dasubuvir, Sofosbuvir
NS5A inhibitors:
Ledipasvir, Ombitasvir, Daclatasvir, Elbasvir, Velpatasvir, Pibrentasvir
Translation
RNA replication
NS3/4A protease inhibitors:
Telaprevir, Boceprevir, Simeprevir, Paritaprevir, Grazoprevir, Voxilaprevir, Glecaprevir
Polyprotein processing
NS5A inhibitors:
Ledipasvir, Ombitasvir, Daclatasvir, Elbasvir, Velpatasvir, Pibrentasvir
HCV NS proteins
Nucleus

PRIMARY GOAL FOR TREATMENT-

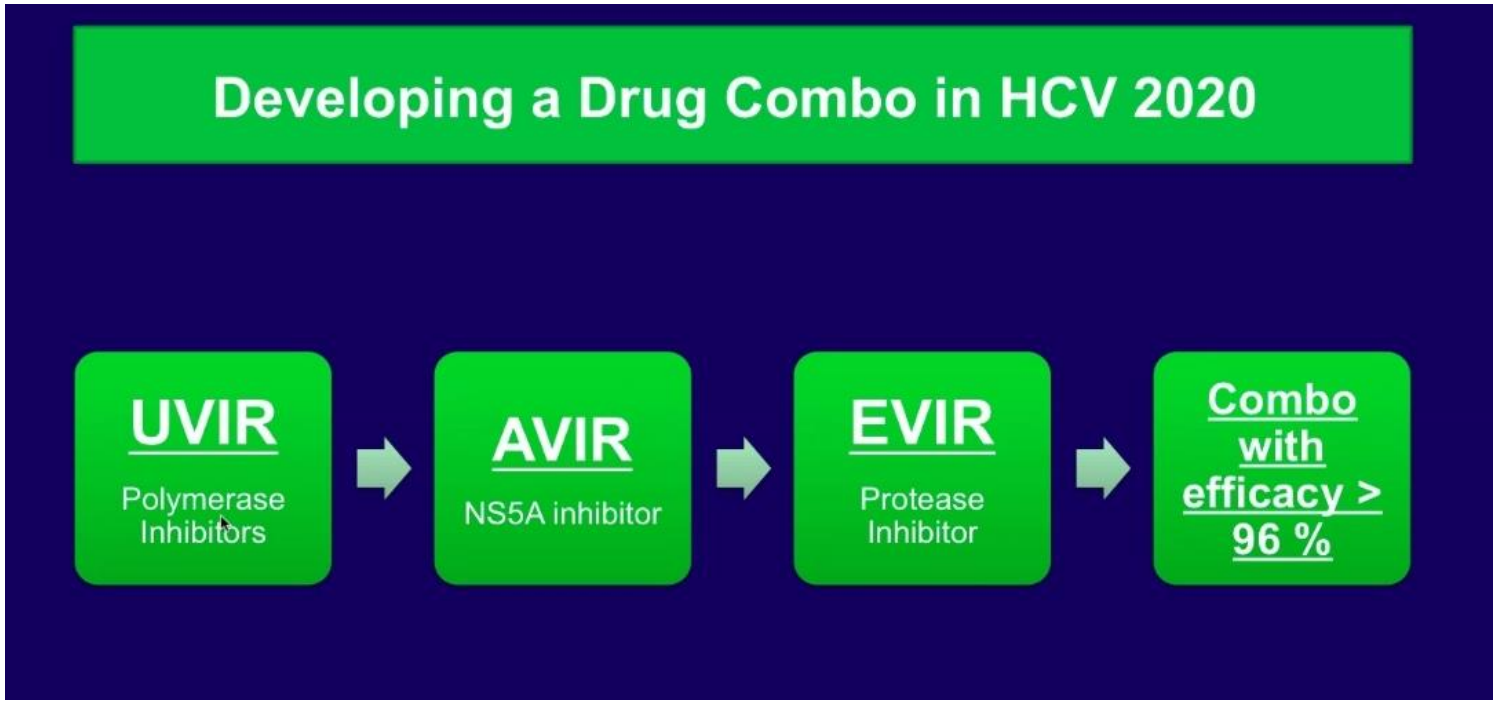
. VIRAL ERADICATION

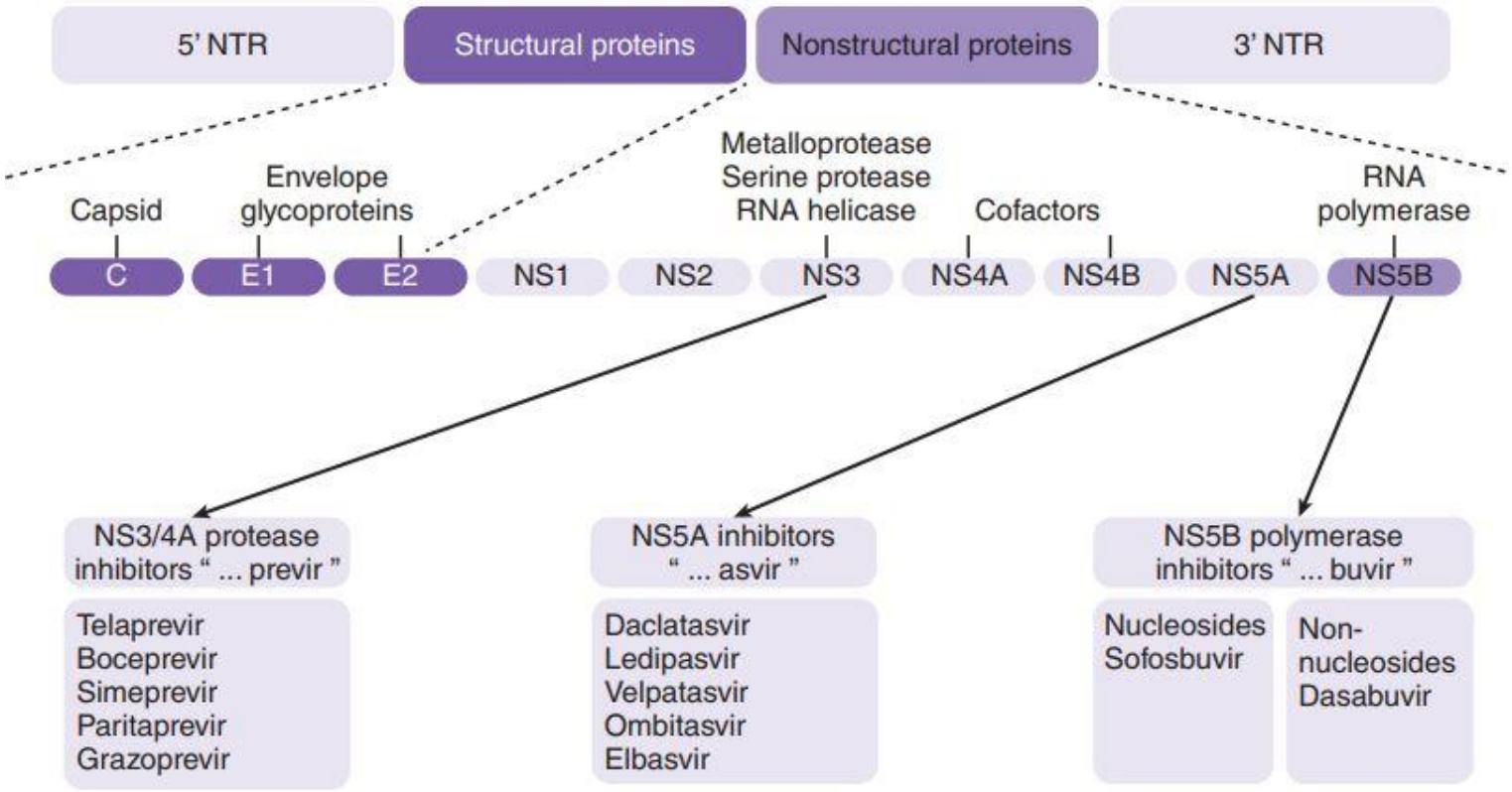
HCV

Chronic:

- interferon alpha 2, pegylated interferon 2a
- ribavirin

- **DAA (direct acting antiviral)**


Developing a Drug Combo in HCV 2020
UVIR
Polymerase Inhibitors
AVIR
NS5A inhibitor
EVIR
Protease Inhibitor
Combo with efficacy > 96 %


5' NTR
Structural proteins
Nonstructural proteins
3' NTR
Capsid
Envelope glycoproteins
Metalloprotease
Serine protease
RNA helicase
Cofactors
RNA polymerase
C
E1
E2
NS1
NS2
NS3
NS4A
NS4B
NS5A
NS5B
NS3/4A protease inhibitors " ... previr "
Telaprevir
Boceprevir
Simeprevir
Paritaprevir
Grazoprevir
NS5A inhibitors " ... asvir "
Daclatasvir
Ledipasvir
Velpatasvir
Ombitasvir
Elbasvir
NS5B polymerase inhibitors " ... buvir "
Nucleosides
Sofosbuvir
Non-nucleosides
Dasabuvir

HEPATITIS C TREATMENT

- Advent of the first-generation **direct-acting antiviral agents (DAAs)** boceprevir and telaprevir dramatically altered the landscape for the optimal treatment of chronic HCV infection, which was previously treated with the combination of interferon- alfa (replaced by pegylated interferon-alfa) and ribavirin.

- **Main targets of the DAAs** are the **HCV-encoded proteins that are vital to the replication of the virus.**

1. **NS5A Inhibitors**

Daclatasvir is used in combination with **sofosbuvir** for treatment of HCV genotypes 1, 2, and 3.

MOA

- The NS5A protein plays a role in both **viral replication and the assembly of HCV**; however, the exact mechanism of action of the HCV NS5A inhibitors remains unclear.

Adverse effects

- headache and fatigue, usually mild or moderate in severity.

NS5B RNA POLYMERASE INHIBITORS

Mechanism of action

- **NS5B is an RNA- dependent RNA polymerase** involved in post-translational processing that is necessary for replication of HCV.

- Nucleoside/nucleotide analogs (**eg, sofosbuvir)** target the catalytic site of NS5B, and are activated within the hepatocyte through phosphorylation to nucleoside triphosphate, which competes with nucleotides, resulting in chain termination.
- Non-nucle- oside analogs **(eg, dasabuvir)** act as allosteric inhibitors of NS5B.

Side effects with elbasvir/grazoprevir

- fatigue, headache, and nausea. Elevations in serum aminotransferases may occur.

TABLE 49–7 **Direct-acting antiviral combination regimens for the treatment of chronic hepatitis C infection in adult patients without cirrhosis.[1]**

Regimen	Class of Agent(s)	HCV Genotype(s)
Velpatasvir 100 mg /sofosbuvir 400 mg once daily × 12 weeks	NS5A inhibitor/NS5B polymerase inhibitor	1, 2, 3, 4, 5, 6
Elbasvir 50 mg/grazoprevir 100 mg once daily × 12 weeks[2]	NS5A inhibitor/NS 3/4A protease inhibitor	1a, 1b, 4
Ledipasvir 90 mg/sofosbuvir 400 mg once daily × 12 weeks	NS5A inhibitor/NS5B polymerase inhibitor	1a, 1b, 4, 5, 6
Paritaprevir 150/ritonavir 100/ombitasvir 25 once daily plus dasabuvir 250 mg bid plus weight-based ribavirin × 12 weeks	NS 3/4A protease inhibitor/ NS5A inhibitor plus NS5B polymerase inhibitor plus guanosine analog	1a, 1b
Paritaprevir 150/ritonavir 100/ombitasvir 25 once daily plus weight-based ribavirin × 12 weeks	NS 3/4A protease inhibitor/ NS5A inhibitor plus guanosine analog	4
Simeprevir 150 mg plus sofosbuvir 400 mg once daily × 12 weeks	NS3/4A protease inhibitor plus NS5B polymerase inhibitor	1a, 1b
Daclatasvir 60 mg[3] plus sofosbuvir 400 mg once daily × 12 weeks	NS5A inhibitor plus NS5B polymerase inhibitor	1a, 1b, 2, 3
Sofosbuvir 400 mg once daily plus weight-based ribavirin × 12 weeks	NS5B polymerase inhibitor plus guanosine analog	2, 3

[1] Regimens may differ in the presence of cirrhosis.

[2] As an alternative regimen, elbasvir 50 mg/grazoprevir 100 mg once daily may be given in combination with weight-based ribavirin for 16 weeks.

[3] Dose adjustment may be required if co-administered with a CYP 3A substrate.

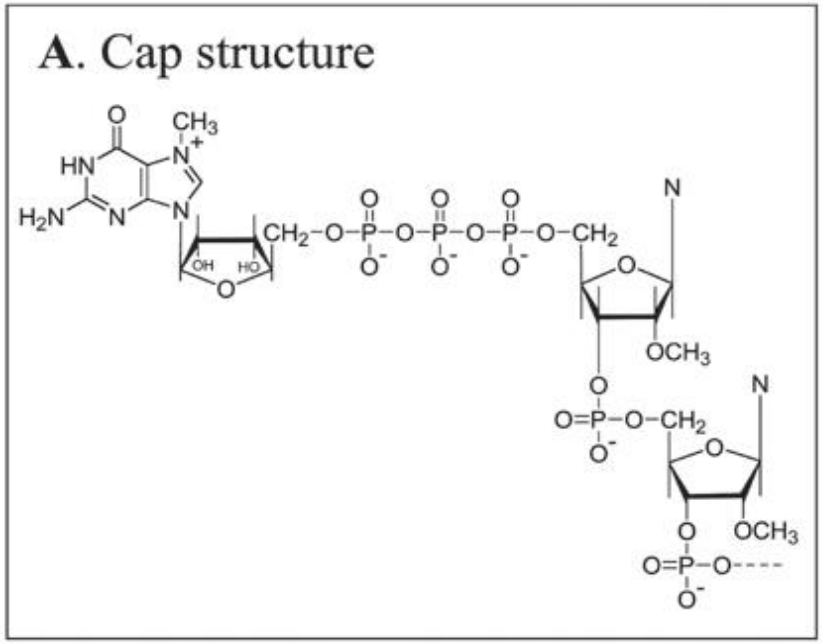
RIBAVARIN (RHINO ,ENTEROVIRUSES ARE RESISTANT)

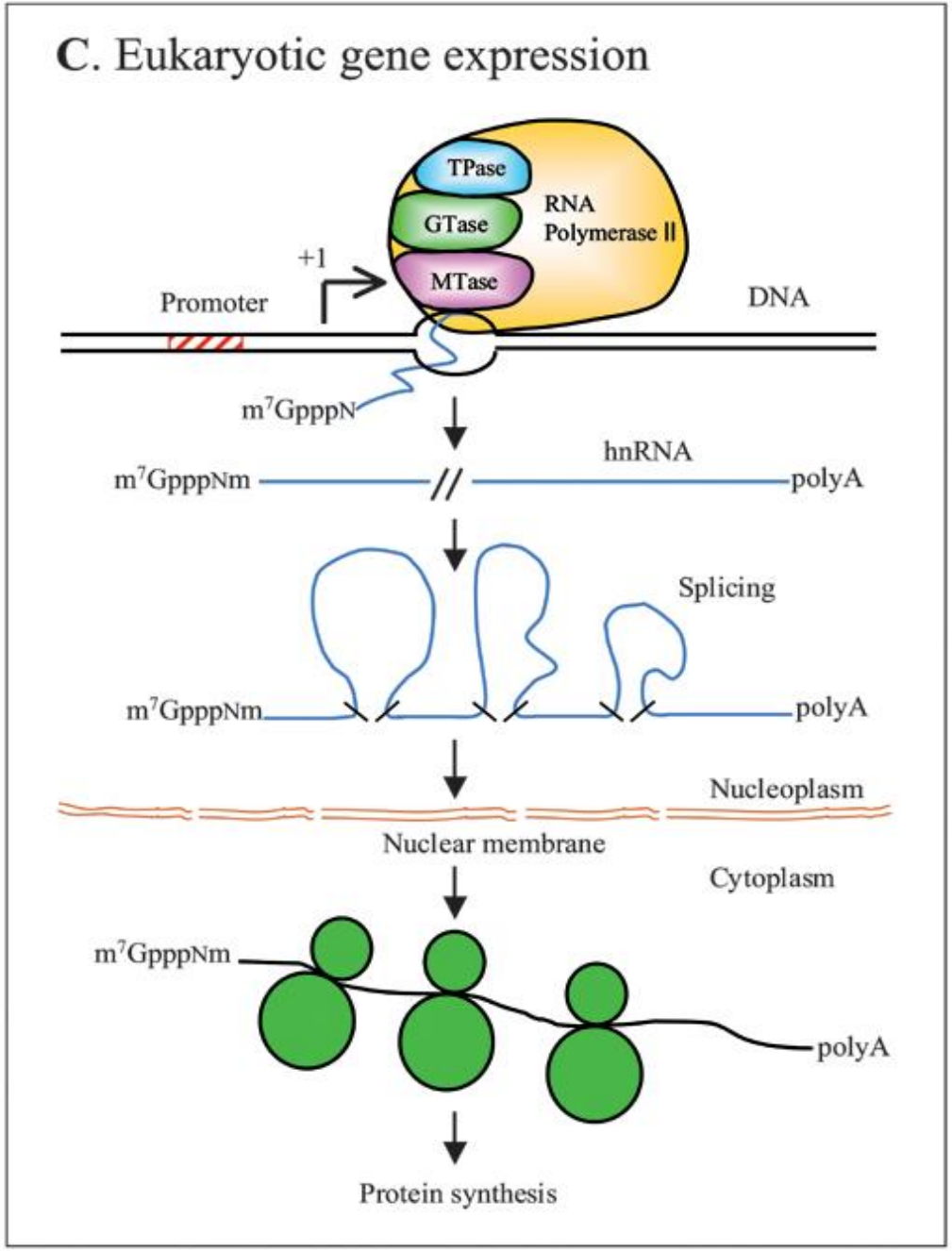
MOA

- phosphorylated-form inhibits GTP
- viral RNA polymerase
- end capping of viral RNA.

P/K

- Oral, IV, aerosol, absorption increased with fatty meals


A. Cap structure
B. Mechanism of cap formation
pppNpNp
Nascent mRNA
RTase
Pi
pppNpNp
GTP
GTase
PPi
G(5')pppNpNp
AdoMet
N7G-MTase
AdoHcy
m7G(5')pppNpNp
(Cap0) RNA
AdoMet
MTase
AdoHcy
m7G(5')pppNmpNp
(Cap1) RNA


C. Eukaryotic gene expression
TPase
GTase
MTase
RNA Polymerase II
+1
Promoter
DNA
m7GpppN
hnRNA
m7GpppNm
polyA
Splicing
m7GpppNm
polyA
Nucleoplasm
Nuclear membrane
Cytoplasm
m7GpppNm
polyA
Protein synthesis

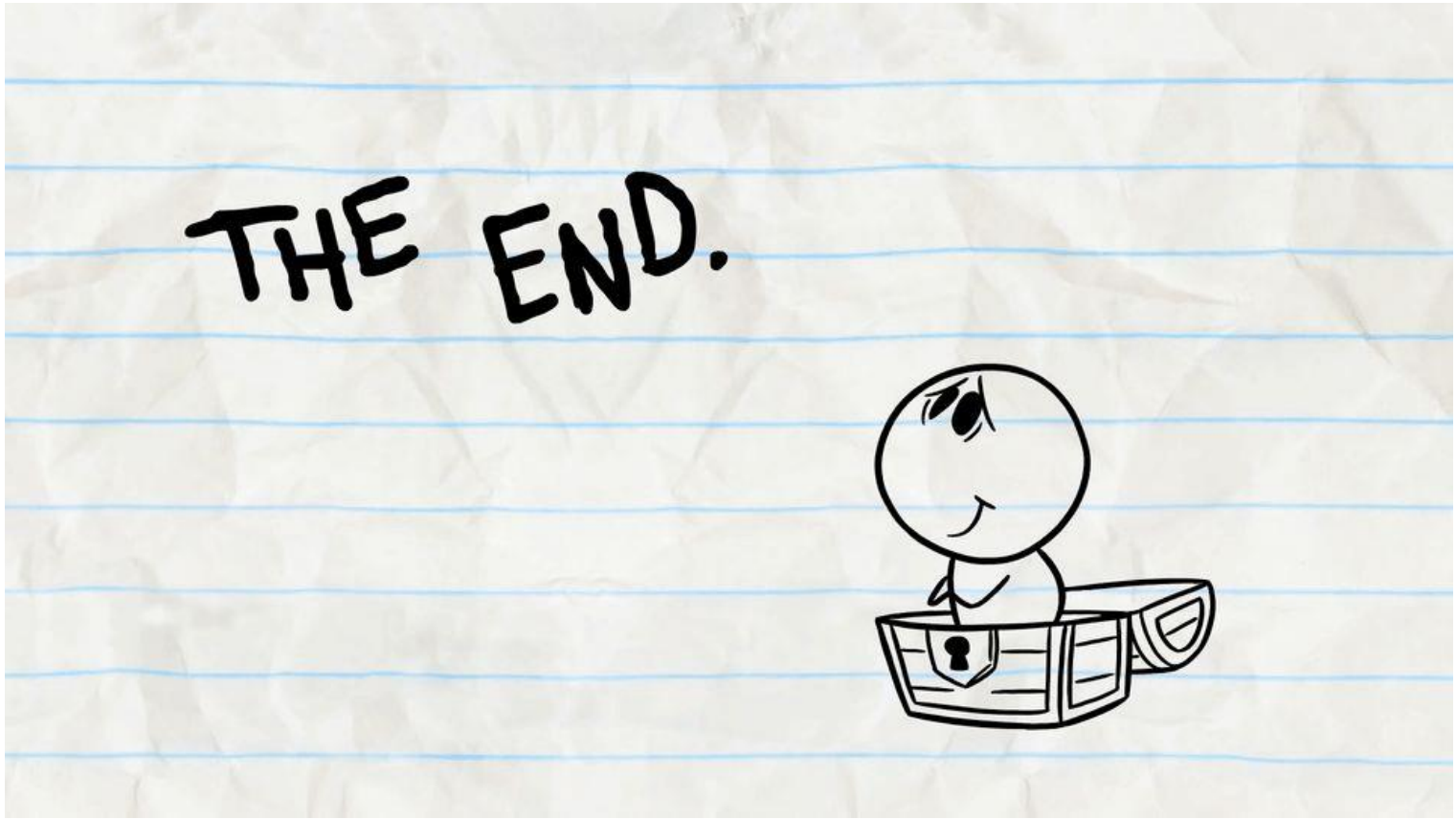
EFFECTIVE ONLY IN COMBO WITH IFN

Clinical Uses:

- RSV, influenza A & B, lassa fever, adjunct to alpha interferon in hepatitis C.

Adverse Effects:

- Heamatotoxicity, upper airway irritation, teratogenic.


THE END.