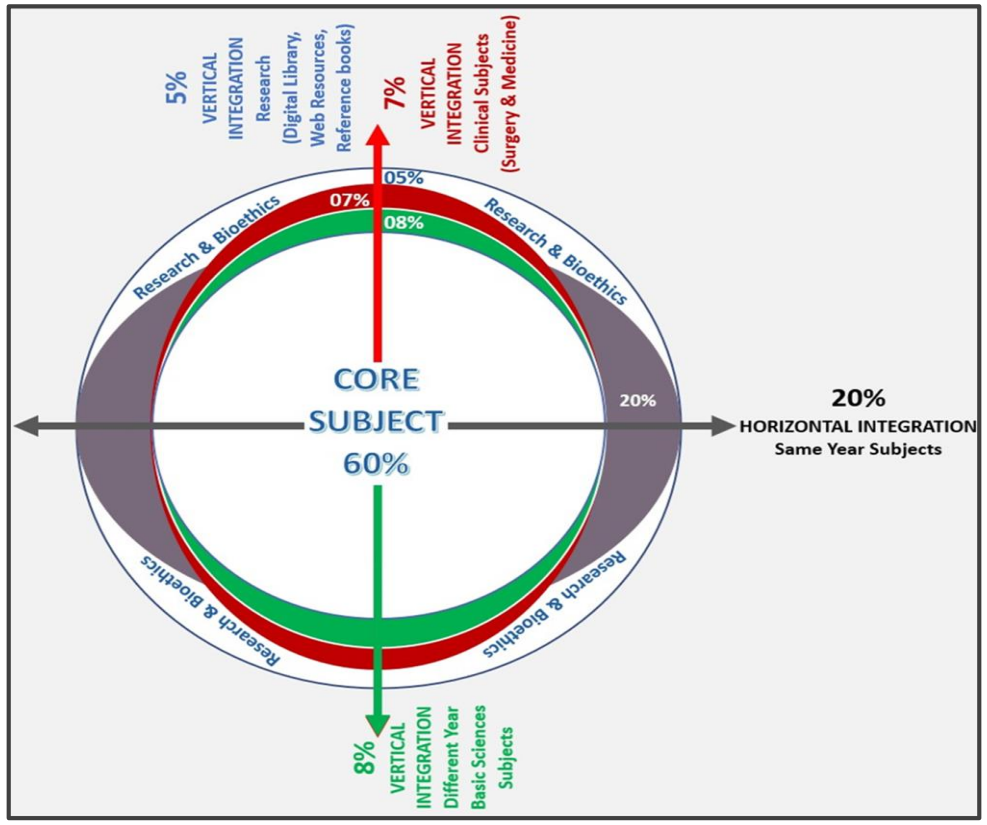
DRUGS USED IN TREATMENT OF VIRAL HEPATITIS (HCV)

Dr. Zunera Hakim

- Katzung's Basic & Clinical Pharmacology, 15th Edition
- Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition

SCHEME OF LECTURE



3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	

LEARNING OBJECTIVES

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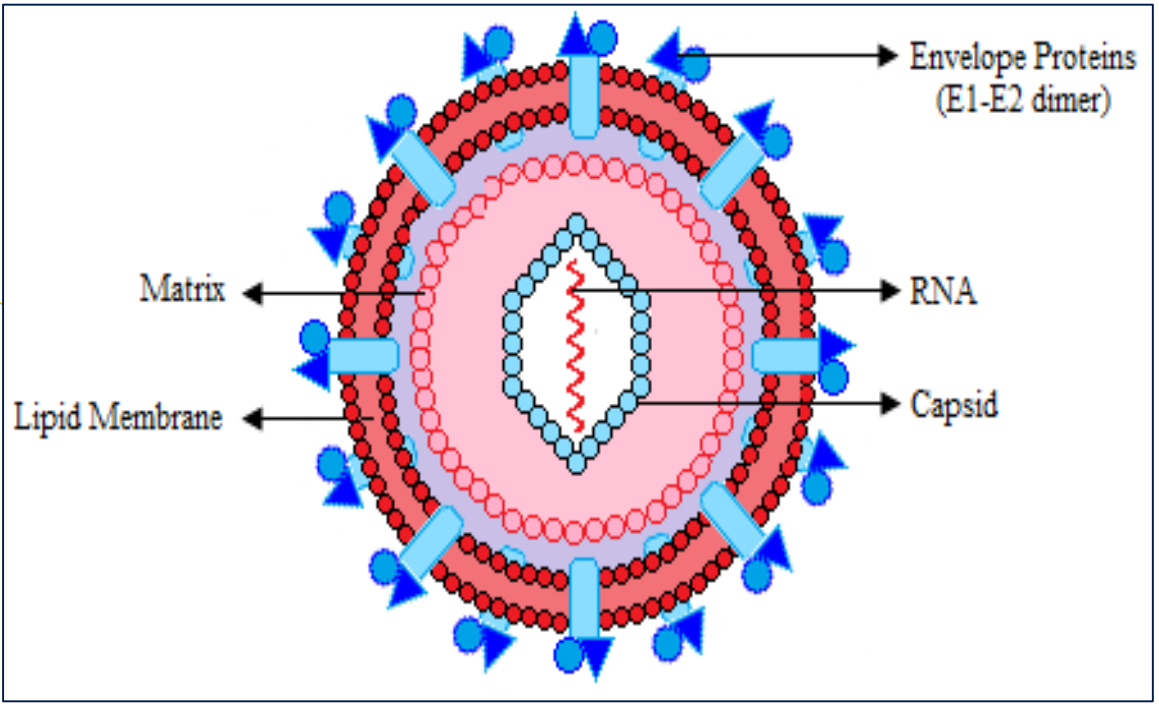
At the end of the lecture, students will be able to:

- Classify antiviral drugs used in the treatment of hepatitis C
- Outline the salient pharmacokinetic & pharmacodynamic features of antiviral drugs used to treat Hep C infections
- Discuss the mechanism of action , adverse effects and contra indications of ribavirin
- Identify the advantages of DAA over interferon based regimens

HEPATITIS C VIRUS

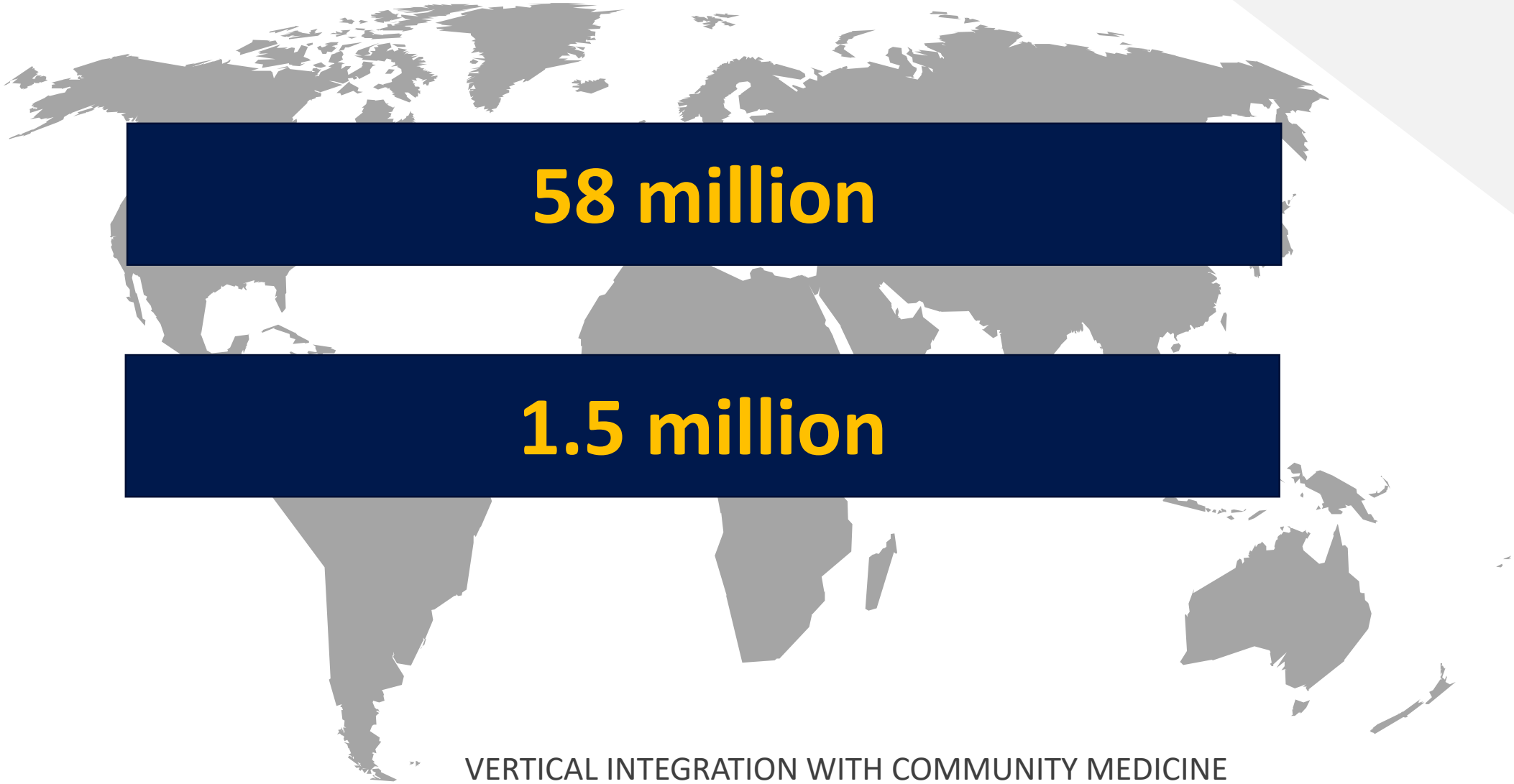
RNA Virus: Hepatitis C Virus



- Post transfusion hepatitis virus, latter termed as Non-A non-B Hepatitis (NANBH) finally termed Hepatitis C in 1989
- Six main genotypes 1,2,3,4 ,5 and 6
- Transmitted via infected blood products, unsterilized instruments and injections, infected mother to child

HORIZONTAL INTEGRATION WITH PATHOLOGY

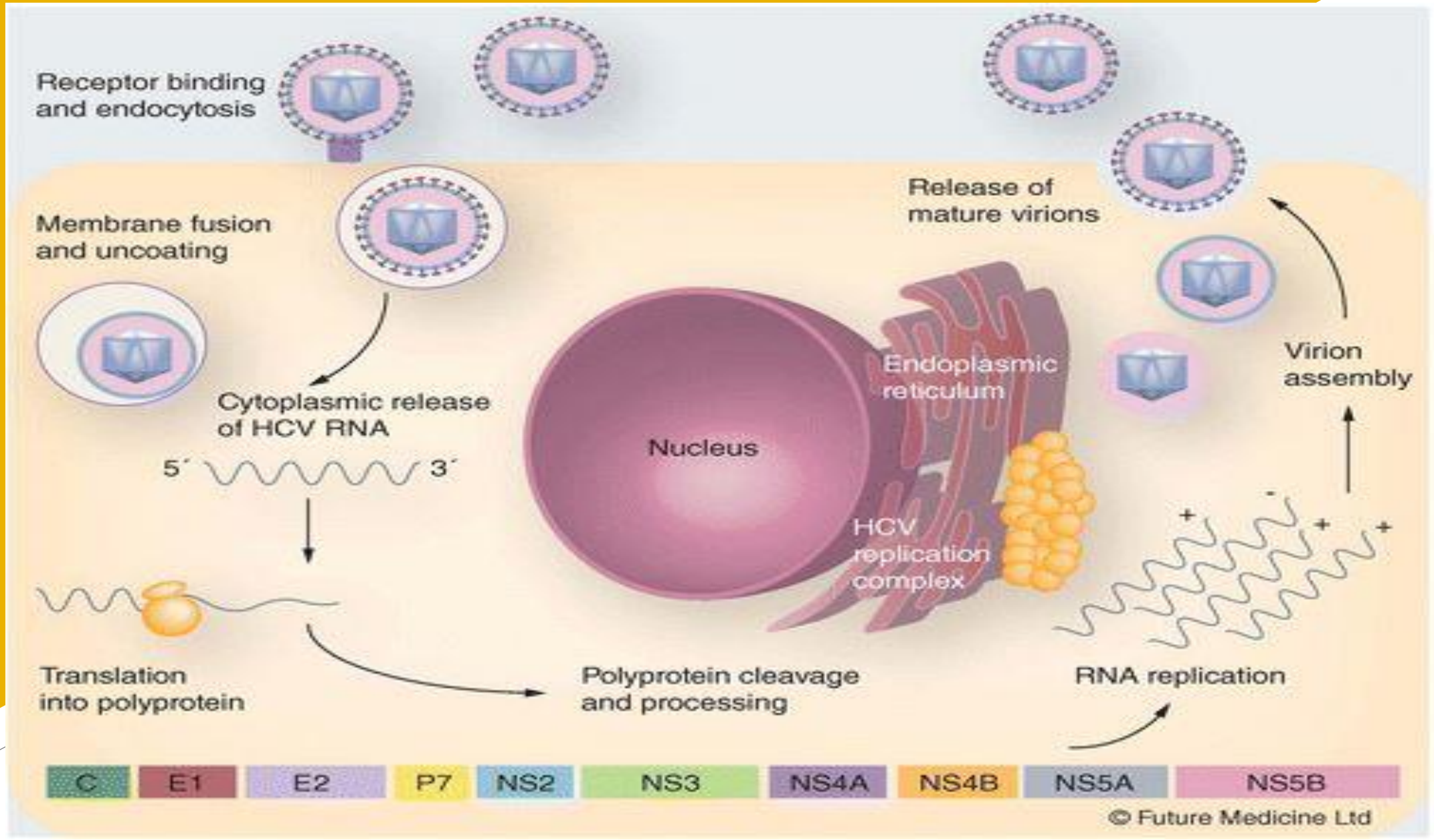
PREVALENCE OF HEPATITIS C



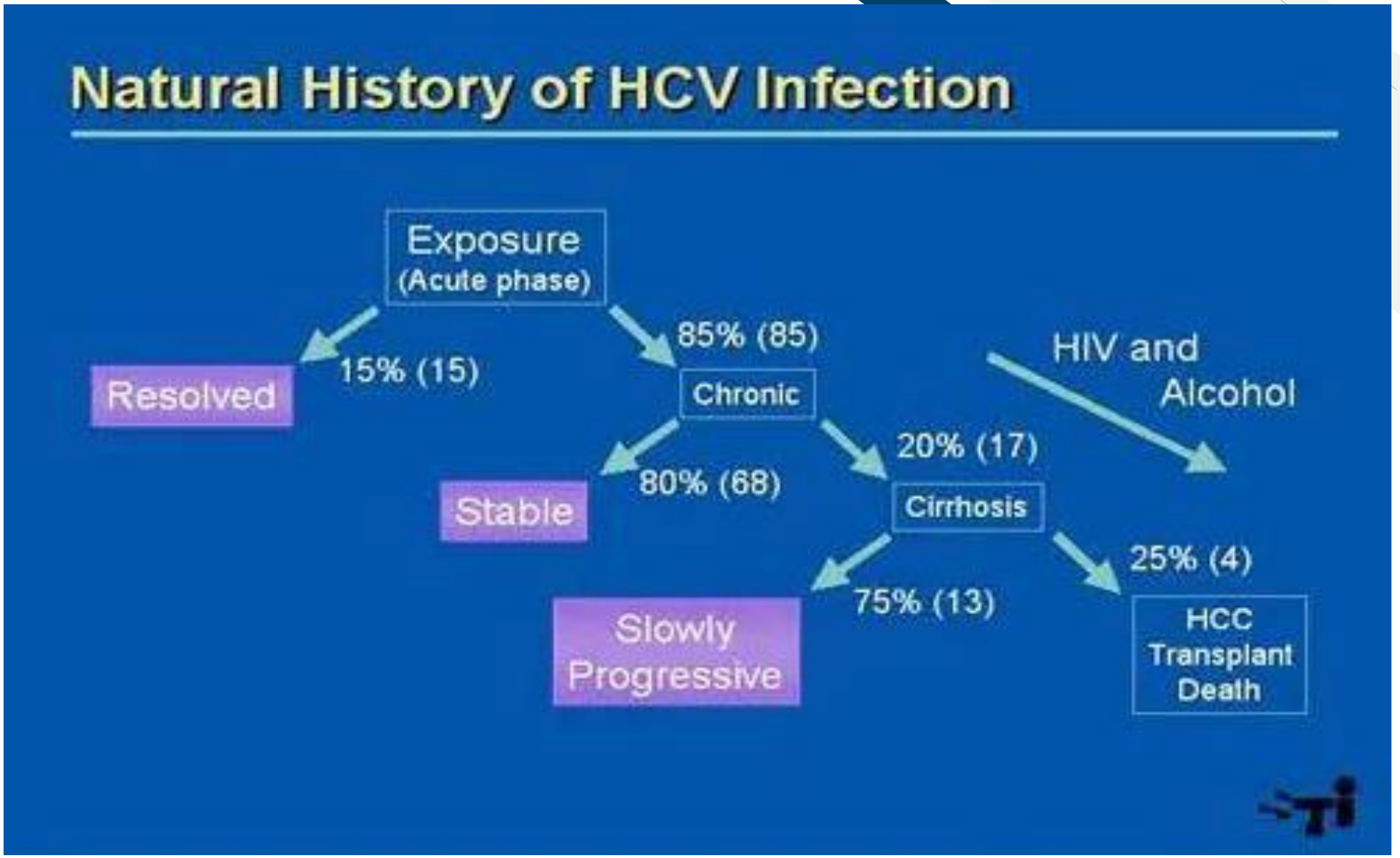
58 million

1.5 million

HCV REPLICATION CYCLE



HORIZONTAL INTEGRATION WITH PATHOLOGY



VERTICAL INTEGRATION WITH MEDICINE

The basics
Hepatitis C treatment

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HEPATITIS C VIRUS TREATMENT

The goals of chronic HCV treatment are:

- To achieve sustained viral response (eradication of infection)
- Inhibit progression to chronic stage

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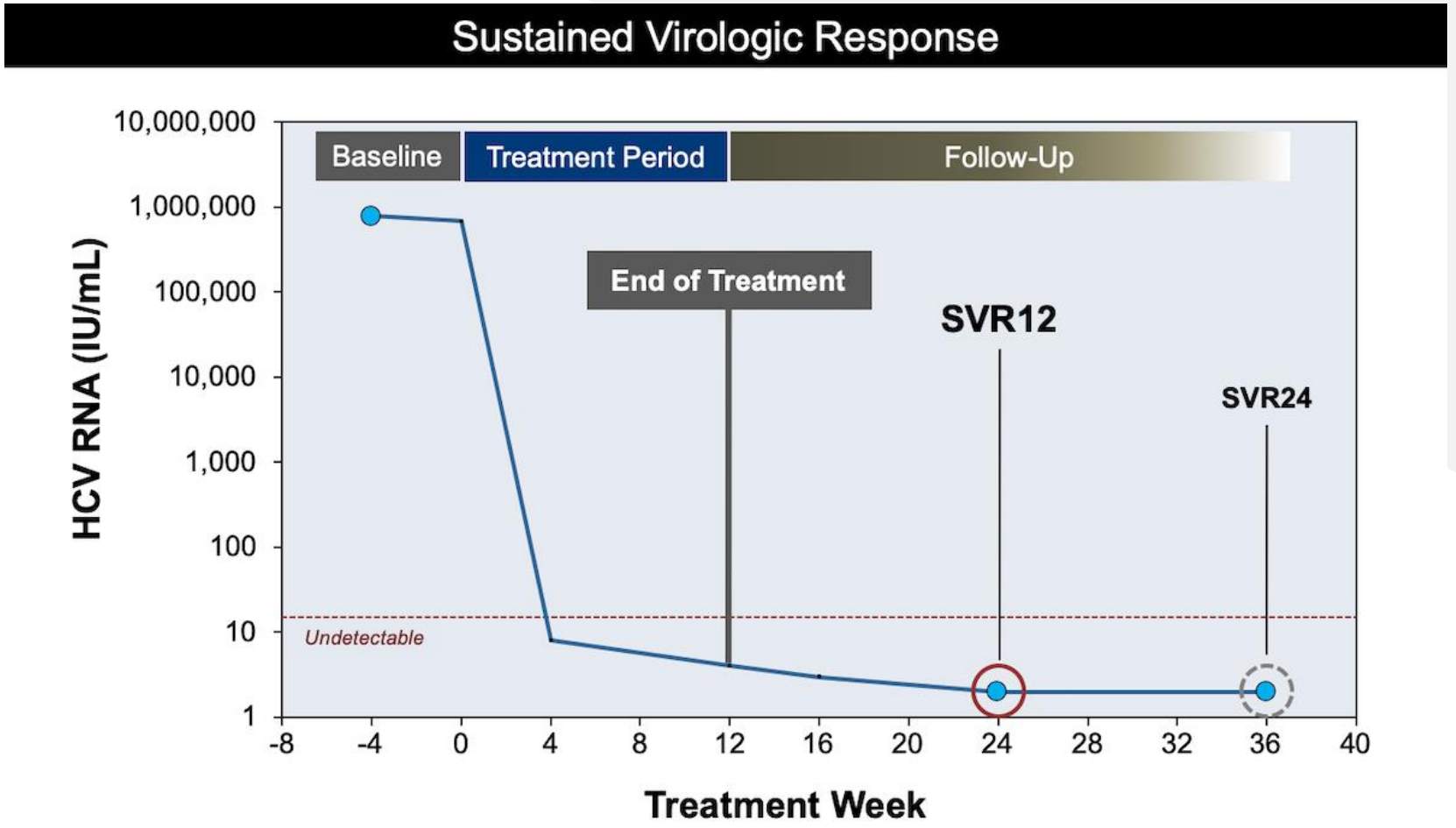
HEPATITIS C VIRUS TREATMENT



DRUGS USED IN HEPATITIS C

1. HOST TARGETING AGENTS

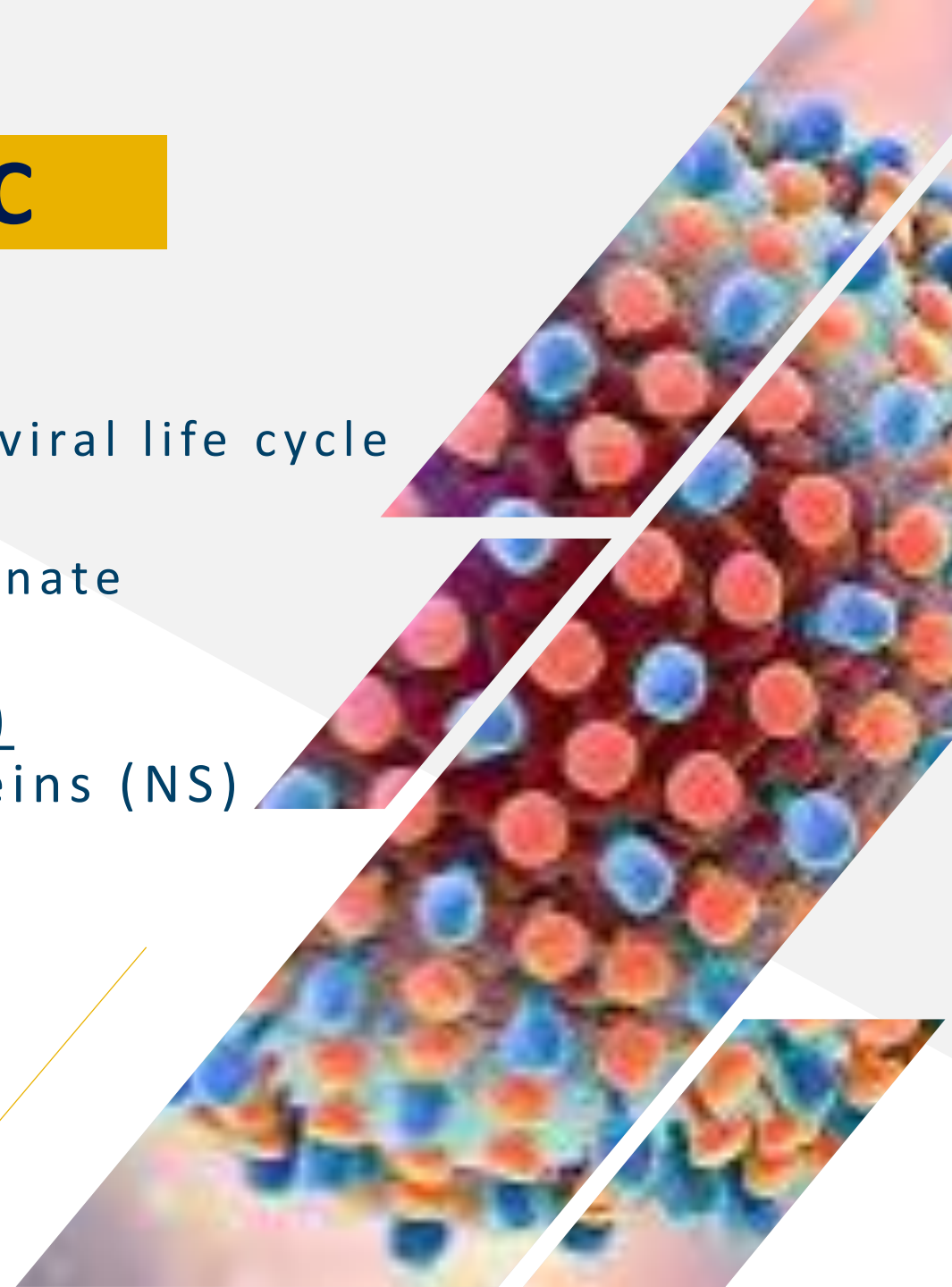
a. Target host factors indispensible for the viral life cycle (host cell entry, replication & assembly

b. Target the host by boosting the host's innate immunity (INF or TLR agonists)

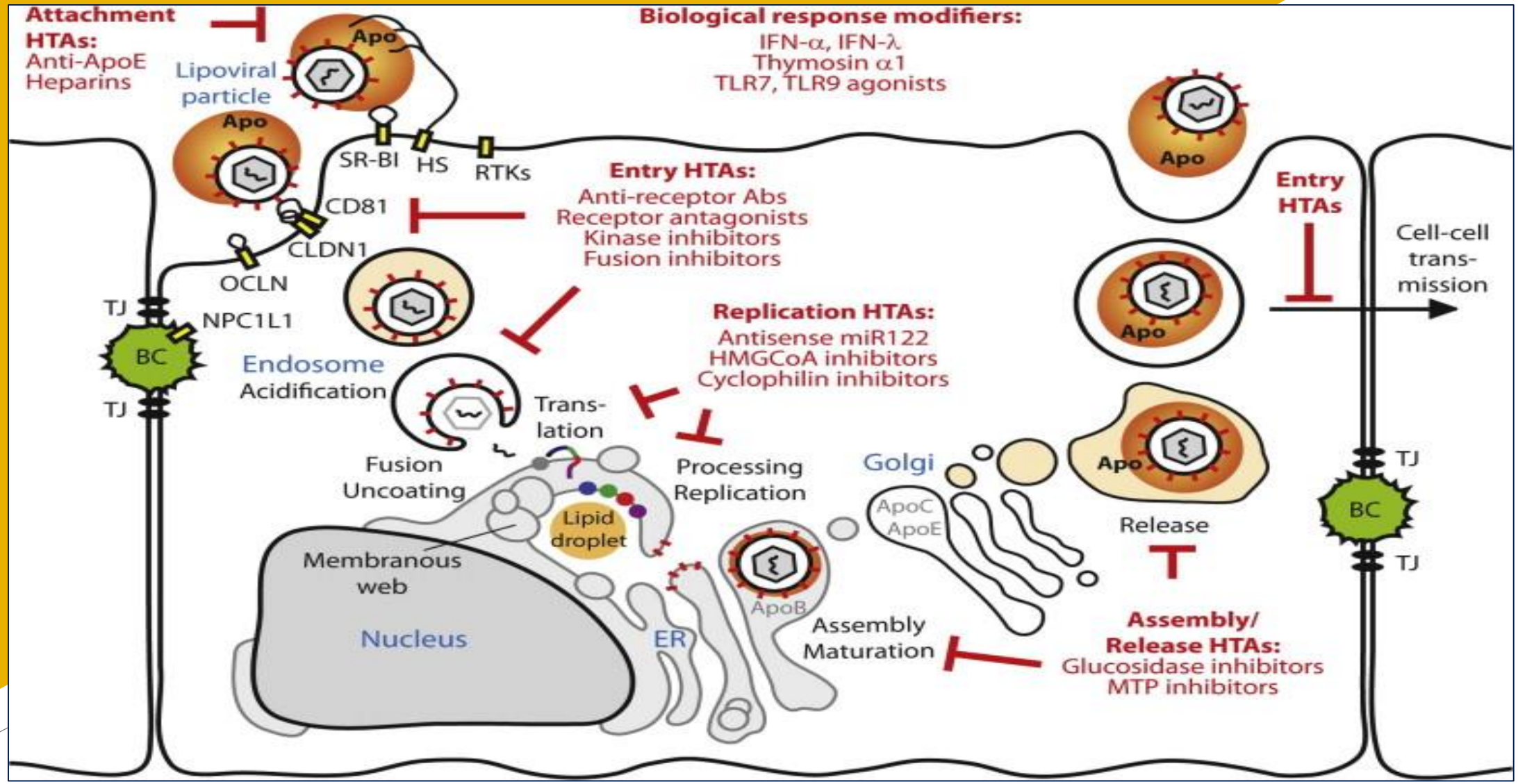
2. DIRECTLY ACTING ANTIVIRALS(DAA)

Inhibit specific HCV non-structural proteins (NS) that are vital for its replication

- NS3/4A Protease inhibitors
- NS5B Polymerase inhibitors (nucleoside & non nucleoside)
- NS5A inhibitors



HOST TARGETING AGENTS USED IN HEPATITIS C



DRUGS USED IN HEPATITIS C

1. INTERFERON ALPHA
2. RIBAVIRIN
3. DIRECTLY ACTING ANTIVIRALS(DAA)

- **NS3/4A Protease inhibitors**
  Boceprevir
  Telaprevir
  Simeprevir
  Asunaprevir
  Grazoprevir
  Paritaprevir
  Volixaprevir
- **NS5B Polymerase inhibitors**
  Nucleosid: Sofosbuvir
  Non nucleoside: Dasabuvir
- **NS5A inhibitors**

  Ombitasvir
  Ledipasvir
  Daclatasvir
  Elbasvir
  Velpatasvir

RIBAVIRIN

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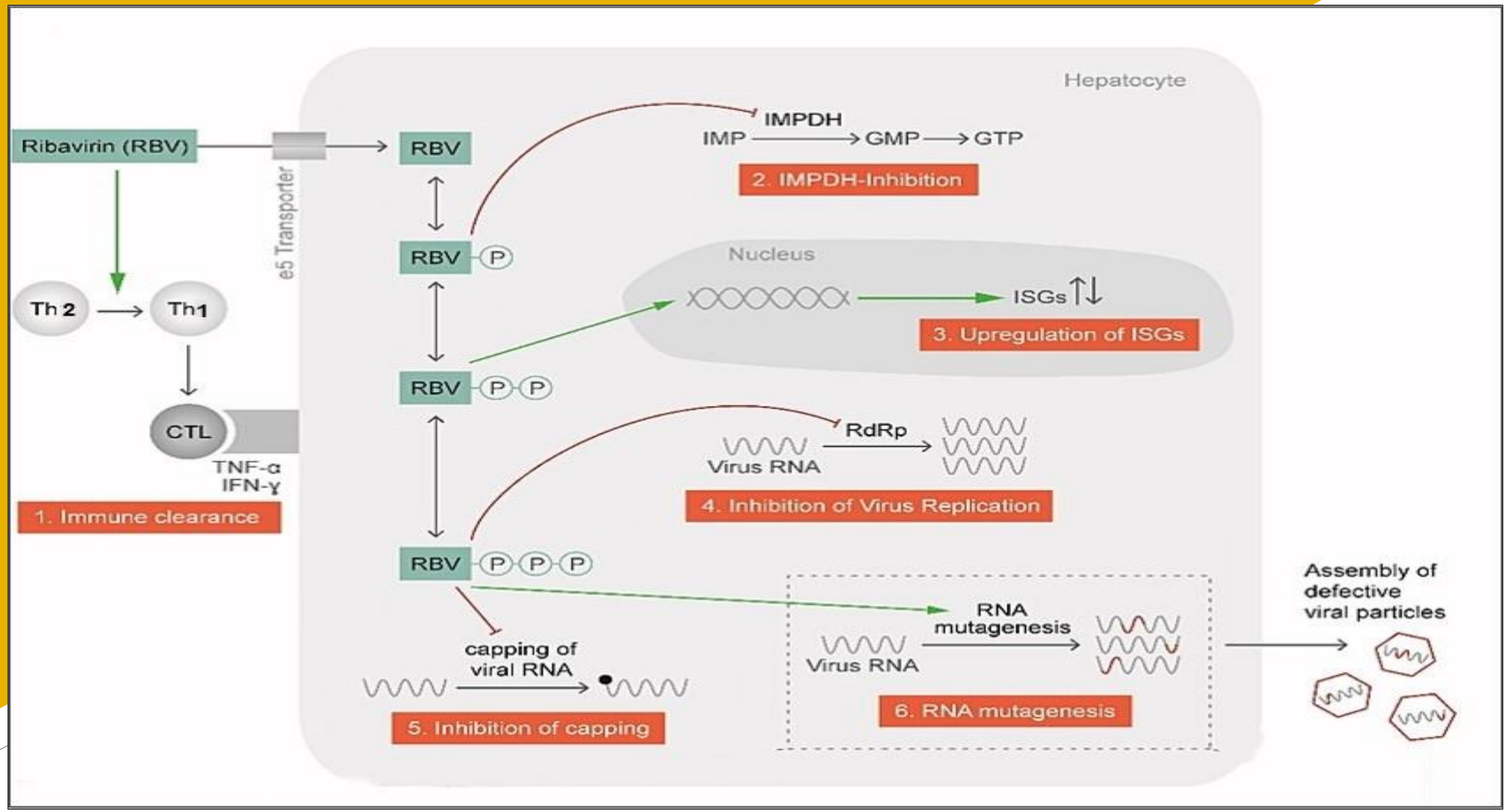
Synthetic guanosine analog
HCV, HIV, influenza A &B, parainfluenza, RSV

- Ribavirin is phosphorylated intracellularly by host cells to triphosphate which causes:
    1. Depletion of guanosine triphosphate (inosine monophosphate dehydrogenase)
    2. Inhibition of viral mRNA capping (triphosphate)
    3. Inhibition of RNA dependent polymerase
    4. Enhancement of viral mutageneis
    5. Induction of IFN stimulated genes

MECHANISM OF ACTION



RIBAVIRIN

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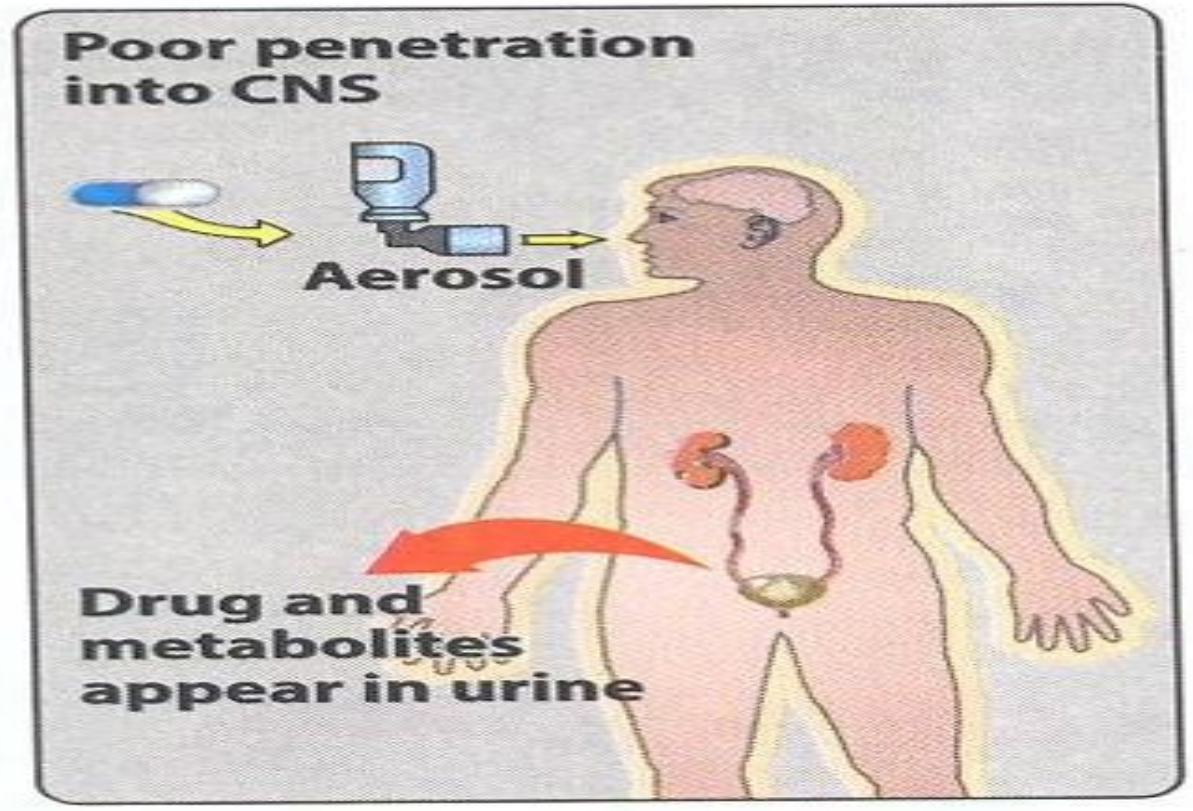
PHARMACOKINETICS

- Oral, IV and aerosol
- BA 45-64 %
- Widely distributed through transporters
- Half life 7-10 days
- Renal elimination



RIBAVIRIN

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THERAPEUTIC USES

- Hepatitis C infection
- Respiratory syncytial viral pneumonia and bronchitis (aerosolized)
- Influenza A & B infection & parainfluenza infection (aerosolized)
- I/V Ribavirin ↓ mortality in lassa fever & haemorrhagic fever if started
- Severe measles pneumonitis

RIBAVIRIN

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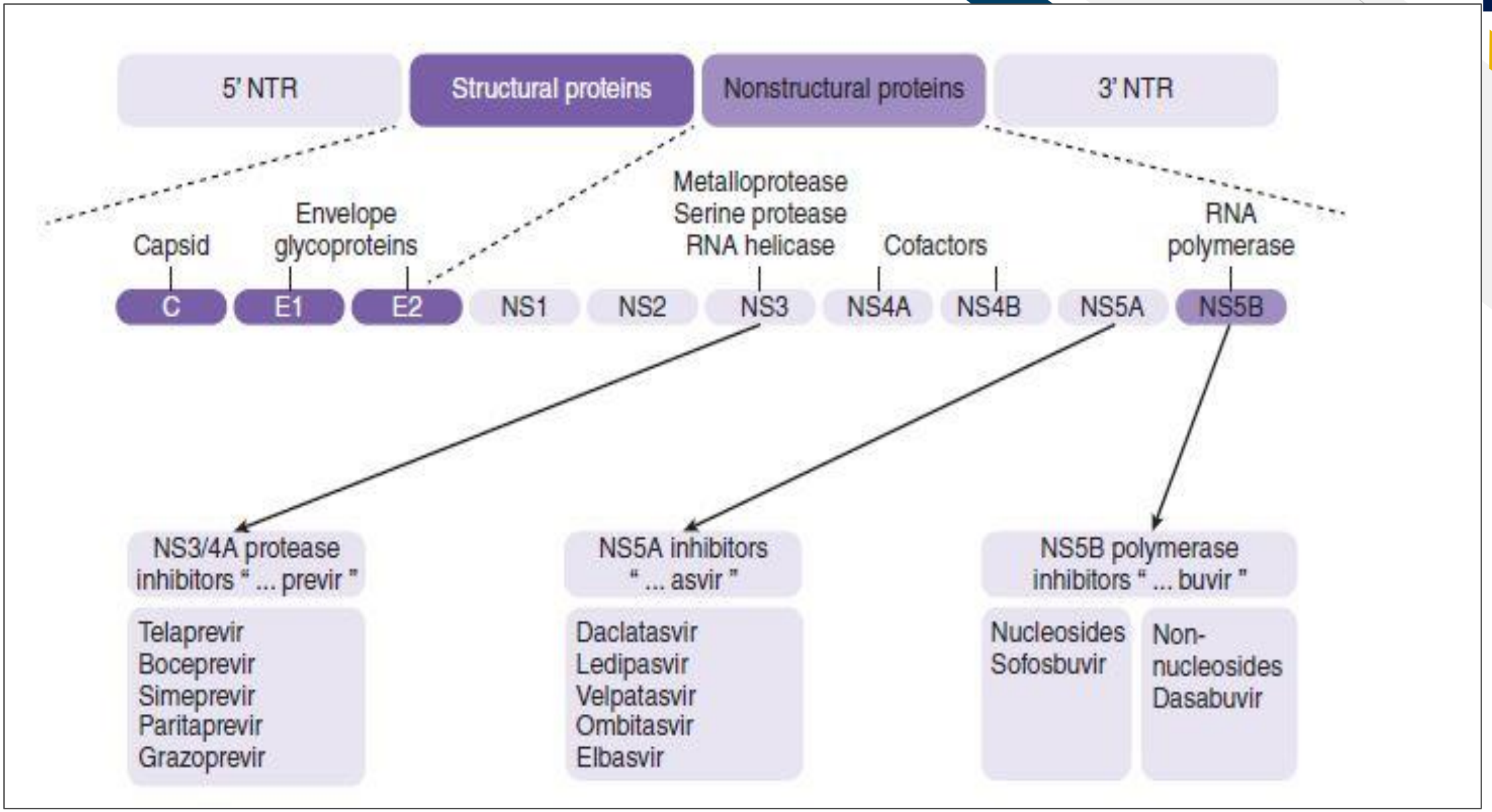
ADVERSE EFFECTS

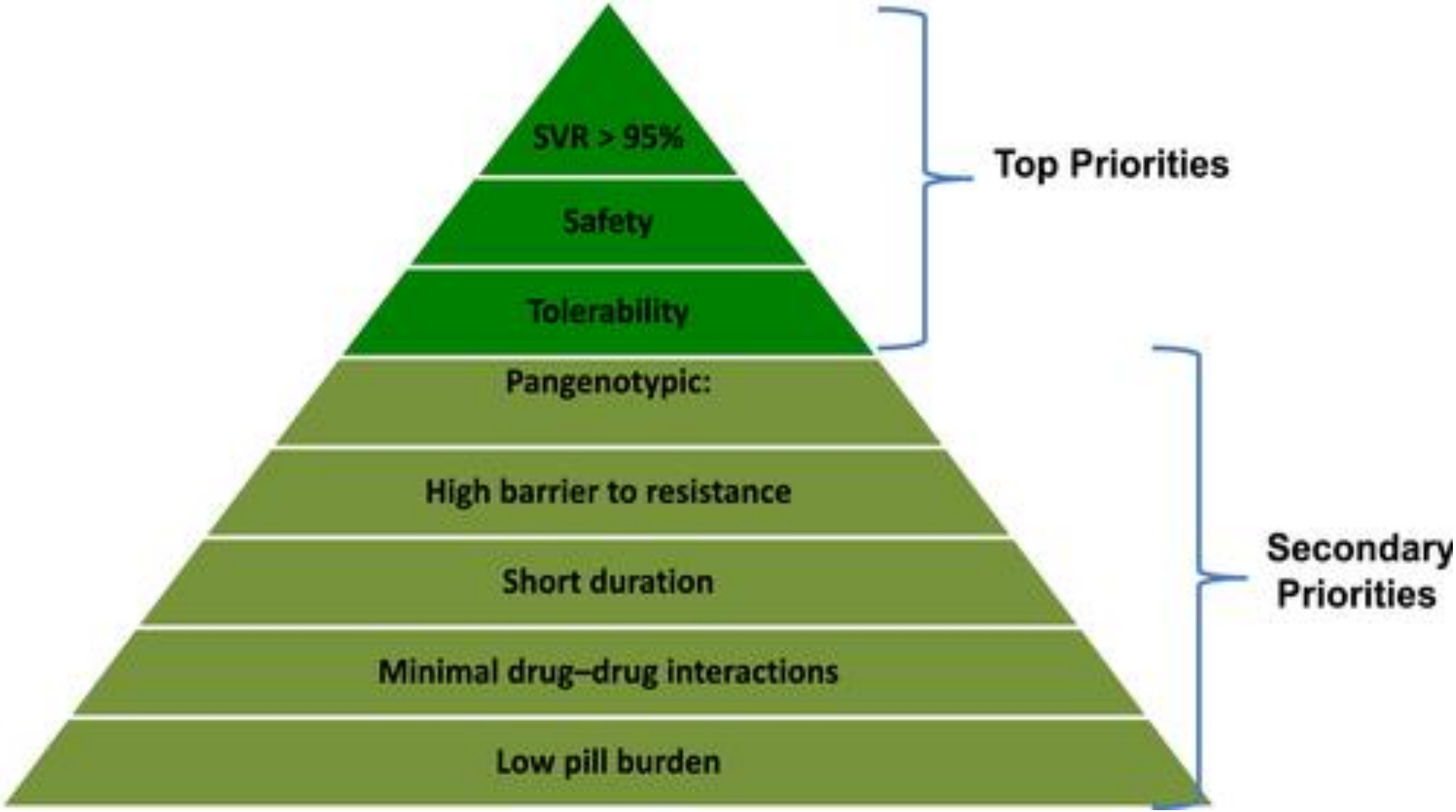
- Dose dependent hemolytic anemia
- Depression ,irritability and insomnia
- Fatigue
- Rash & pruritis
- Cough and transient wheezing
- Conjunctival or bronchial irritation (aerosolized)
- Precipitation on contact lens, plugging of valves & tubings
- Teratogenic

CONTRAINDICATIONS

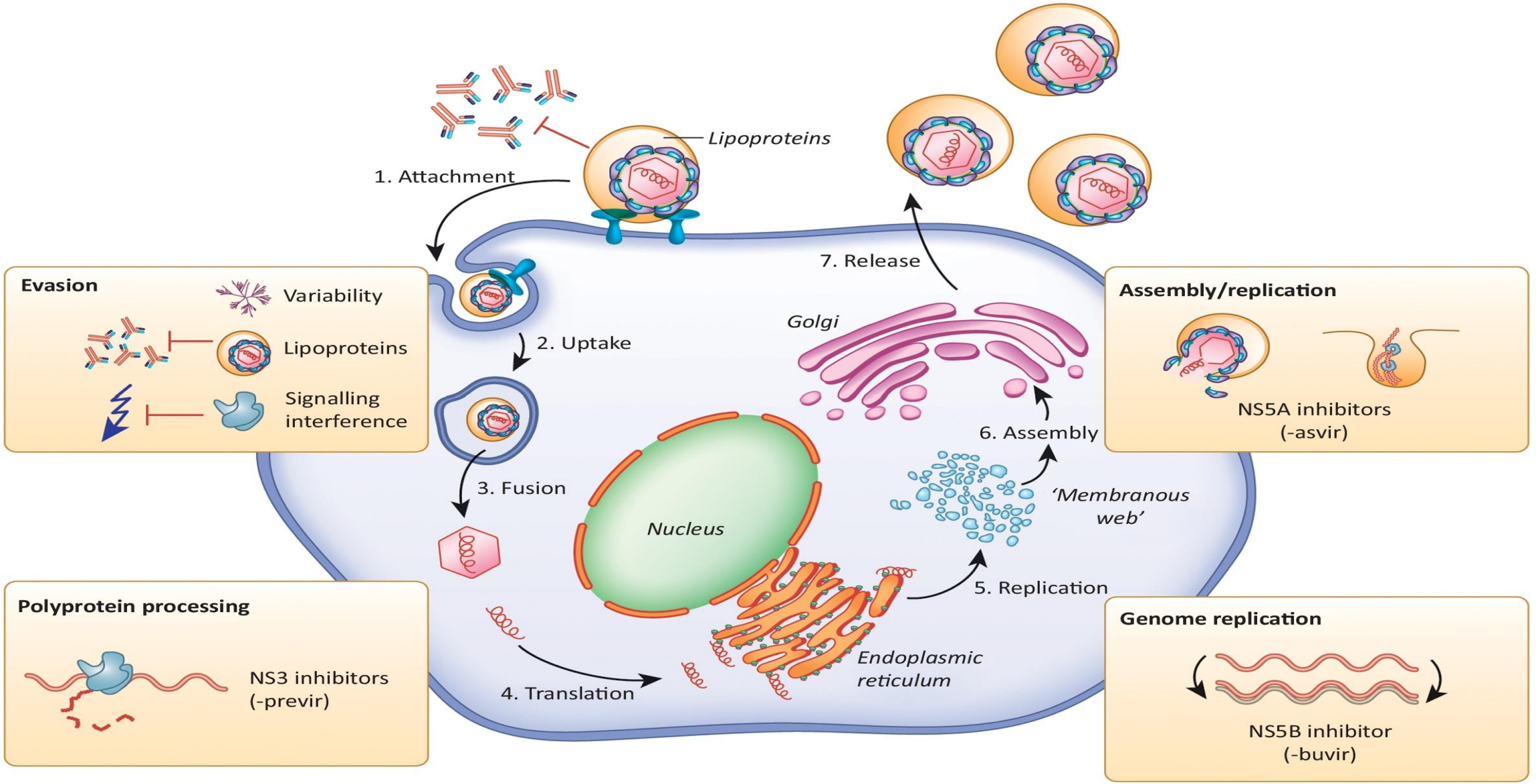
- Anemia
- Renal failure
- Ischemic vascular disease
- Pregnancy


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

DIRECTLY ACTING ANTIVIRALS



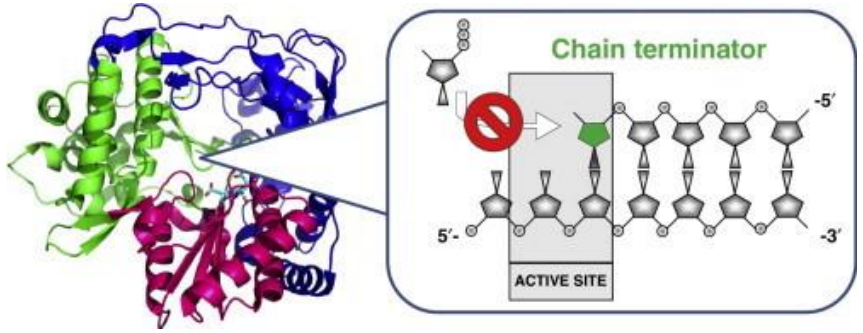
MECHANISM OF ACTION OF DAA

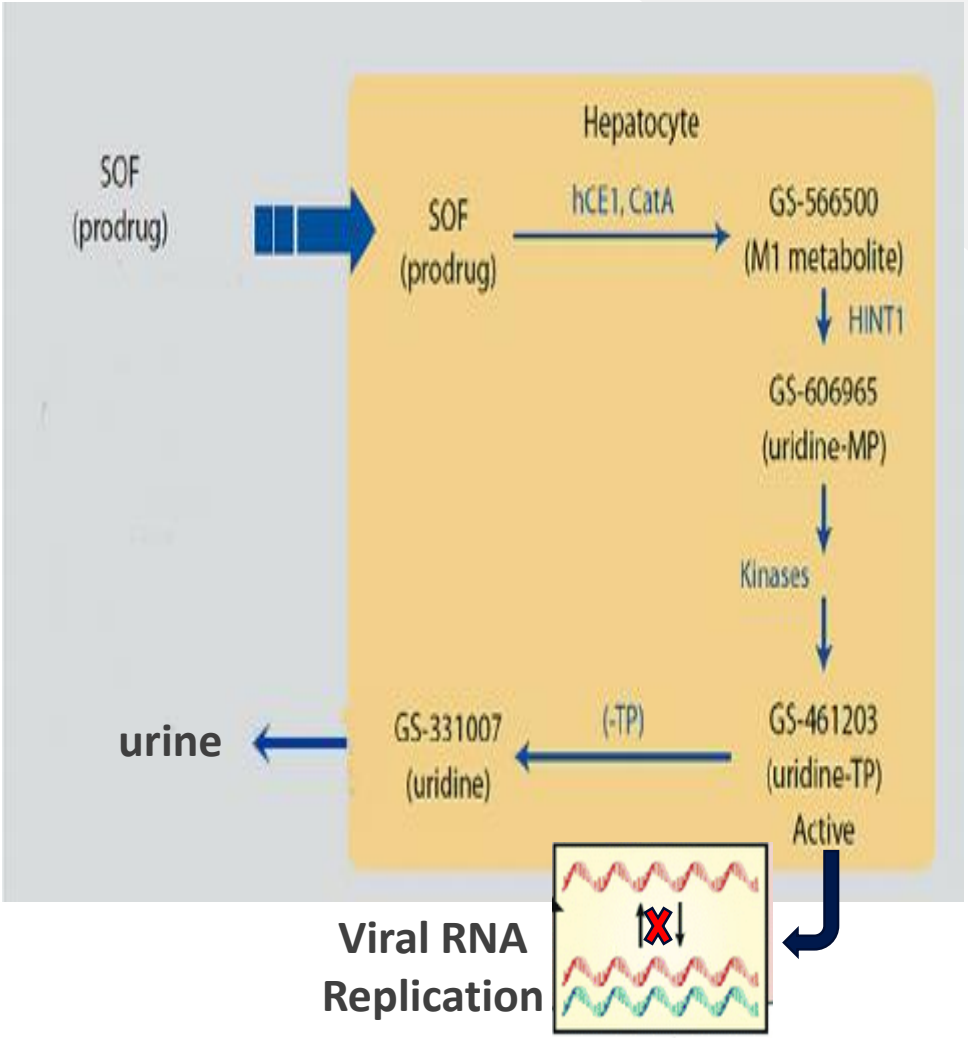


NS5B POLYMERASE INHIBITORS

SOFOSBUVIR

- Pangenotypic
- Sofosbuvir is a uridine nucleotide prodrug which is phosphorylated to its active form in the hepatocytes.
- The active form competes with natural nucleotides causing termination of HCV-RNA replication.





3. NS5B POLYMERASE INHIBITORS

NS5B Polymerase Inhibitors					
Nucleoside Inhibitors					
Sofosbuvir	Food ↔	PPB 61-65% Substrate of P-gp and BCRP	Prodrug is phosphorylated to active-form	ND	Renal
Non-Nucleoside Inhibitors					
Dasabuvir	↑ by food	PPB 99% substrate of P-gp and BCRP	CYP2C8 CYP3A, CYP2D6	ND	Hepatic

- Associated with no significant adverse effects itself
- ADRs arise when administered as part of combination DAA treatment (bradycardia with amiodarone)

RESEARCH

- Page K, Melia MT, Veenhuis RT, Winter M, Rousseau KE, Massaccesi G, Osburn WO, Forman M, Thomas E, Thornton K, Wagner K, Vassilev V, Lin L, Lum PJ, Giudice LC, Stein E, Asher A, Chang S, Gorman R, Ghany MG, Liang TJ, Wierzbicki MR, Scarselli E, Nicosia A, Folgori A, Capone S, Cox AL. **Randomized Trial of a Vaccine Regimen to Prevent Chronic HCV Infection. N Engl J Med**. 2021 Feb 11;384(6):541-549. doi: 10.1056/NEJMoa2023345. PMID: 33567193; PMCID: PMC8367093.

- Calleja, J.L., Aguilera, A., Buti, M. *et al.* Ten steps to eliminating hepatitis C in hospitals. *Nat Rev Gastroenterol Hepatol* **19**, 481–483 (2022). https://doi.org/10.1038/s41575-022-00647-1

- Feld, J. J. et al. Short-course, direct-acting antivirals and ezetimibe to prevent HCV infection in recipients of organs from HCV-infected donors: a phase 3, single-centre, open-label study. *Lancet Gastroenterol. Hepatol.* **5**, 649–657 (2020).

BIOETHICS

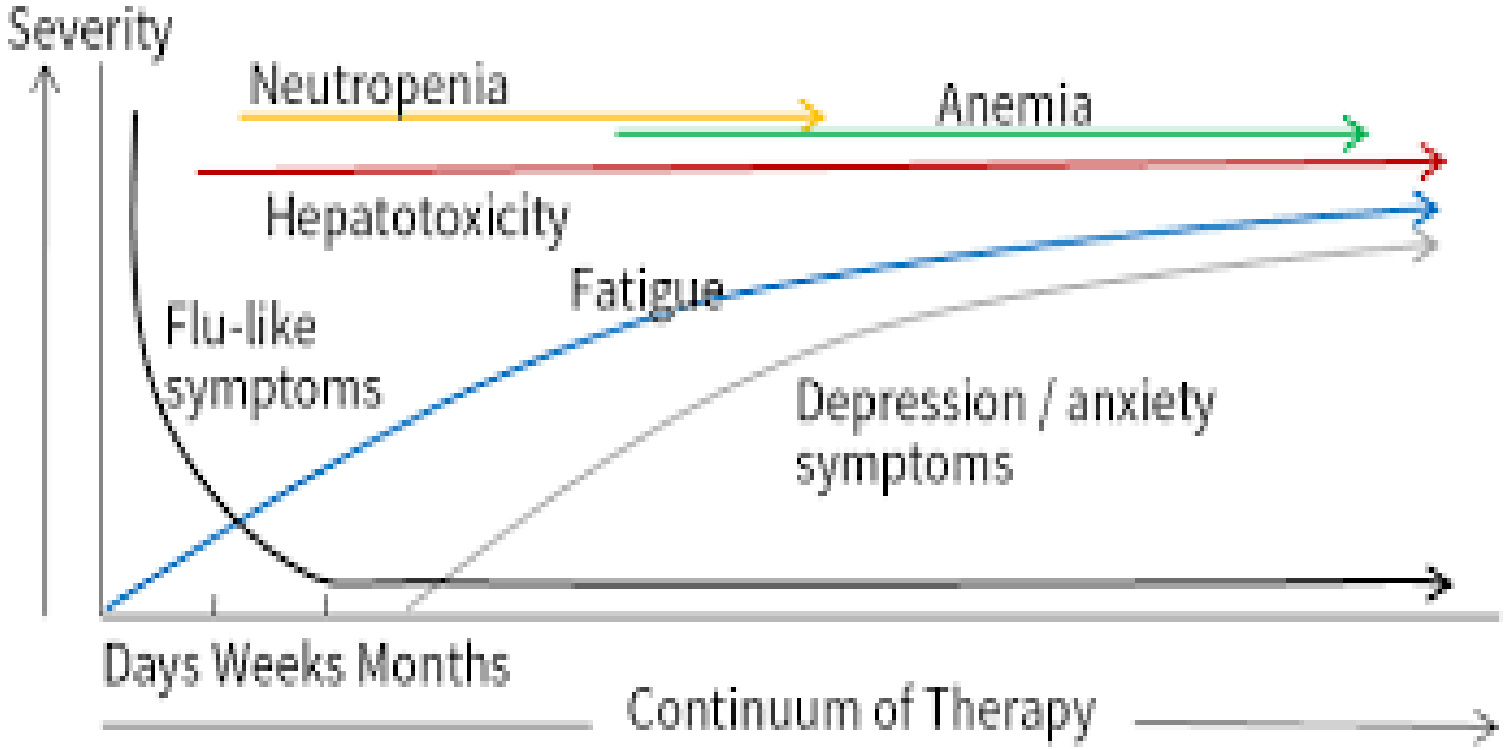
- Clinical trials involving testing newer drugs on humans require informed consent

ARTIFICIAL INTELLIGENCE

- Kashif, A.A., Bakhtawar, B., Akhtar, A., Akhtar, S., Aziz, N. and Javeid, M.S., 2021. Treatment response prediction in hepatitis C patients using machine learning techniques. *International Journal of Technology, Innovation and Management (IJTIM)*, *1*(2), pp.79-89.

- Park, H., Lo-Ciganic, W.H., Huang, J., Wu, Y., Henry, L., Peter, J., Sulkowski, M. and Nelson, D.R., 2022. Machine learning algorithms for predicting direct-acting antiviral treatment failure in chronic hepatitis C: An HCV-TARGET analysis. *Hepatology*, *76*(2), pp.483-491.

END OF LECTURE ASSESSMENT



- Identify the drug most likely responsible for the adverse effects in Fig
- Give the mechanism of action
- Write important clinical indications


Thanks With جَزَاكَ اللَّهُ خَيْرًا
May Allah reward you in goodness