بسم الله الرحمن الرحيم

Treatment of viral hepatitis

by

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REMEMBER THE FOLLOWING ABOUT ANTIHEPATITIS DRUGS

- They are not curative
- They suppress **Viral replication**, put patient in remission, prevent complications.
- Have to be taken for long duration
- Disease can flare up when drugs stopped

- Most drugs are nucleoside/nucleotide analogues
- Most are prodrugs
- Most are converted to phosphate form
- Most inhibit DNA polymerase/RNA polymerase

Drugs treating HBV infection

1- Lamivudine

➢ Cytidine Nucleoside analogue

MOA

Phosphorylated intracellularly.

Inhibits **HBV DNA polymerase**. Causes viral DNA chain termination by getting incorporated into viral DNA.

Use

1. Chronic HBV infection – 100mg OD

✓ Brings about clinical, biochemical , histological improvements but effects not sustained over the years.

✓ Development of resistance within 1-5yrs→**NOT THE FIRST LINE DRUG**

2. HIV - 150-300mg OD (in combination with other anti HIV drugs)

Pharmacokinetics

- Good oral bioavailability
- Plasma T1/2 = 6to 8hrs (t1/2 =12hrs in HBV infected cells)
- Excreted unchanged in urine

ADR

(*Well tolerated*)

- Headache, fatigue
- Nausea, anorexia, abdominal pain
- Rashes
- Pancreatitis, neuropathy (rarely)

❑ **Genetic mutations of HBV DNA polymerase causes resistance to lamivudine.**

❑ **Telbivudine is no longer used in treating HBV.**

2- Entecavir

Guanosine nucleoside analogue with same MOA as Lamivudine

Differences from Lamivudine

- Food decreases oral absorption(administered in empty stomach)
- **T1/2 : 128-148hrs**
- Sleep disturbances & lactic acidosis can be additional ADRs
- **1st line drug for HBV**
  - Rapid clinical, biochemical, histological improvement than Lamivudine
  - Effect sustained
  - Development of resistance rare

3- Adevofir dipivoxil

AMP nucleotide analogue.

Prodrug. Gets activated to Adefovir (by esterases in intestine & liver). MOA same as Lamivudine.

Uses

1. Chronic hepatitis B

- **Not a 1st line drug** as virological response is slow.
- Used mainly in lamivudine resistant cases

4- Tenofovir Disoproxil fumarate

Nucleotide analogue. Prodrug converted to Tenofovir.

Similar to Adefovir but it is **first line drug for HBV** due to its High efficacy, good tolerability & low risk of development of resistance,

Has activity against HIV also (reverse transcriptase inhibitor)

tenofovir alafenamide was associated with less renal and bone toxicity compared with tenofovir disoproxil.

Drugs for HCV

1- Ribavirin

- Guanosine nucleoside analogue
- **Broad spectrum antiviral drug**
  - HCV
  - Influenza A & B
  - Respiratory Syncytial virus (RSV)

MOA

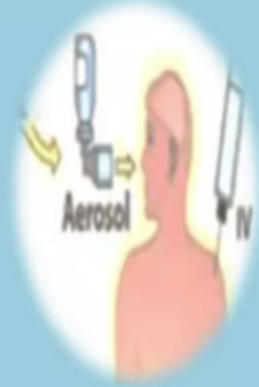
Phosphorylated inside cells

Inhibits RNA polymerase & stops viral RNA replication.

Ribavirin with Azathioprine or zidovudine may cause bone marrow depression

Uses

1. **Chronic Hepatis C** (in combination with interferons or other drugs) (6-12 months)
2. **RSV** Bronchiolitis in children (nebulisation)



ADR

- Hemolytic anemia (dose dependent)
- Bone marrow suppression
- CNS/GIT effects
- Teratogenic (**Females to practice contraception during & till 3months after Ribavirin treatment)**

- Bronchoconstriction (avoided in asthmatics)

Interferon (IFN)α

WHAT ARE INTERFERONS ?

Low molecular weight glycoprotein cytokines produced by host cells in response to viral infections, IL-1 & other inducers.

They have antiviral effects & effects on immunity & cell proliferation

3 types of IFN produced by humans — **IFNα** (Clinically used)
IFNβ
IFN γ

PEG-IFN resulted in a **sustained loss of hepatitis B e antigen** (Hbe Ag) in 30% of patients.

Pharmacokinetics of interferone:

-INF is ineffective orally and given by **I.M. or S.C. route**.

-They are inactivated in the body fluids and different tissues including kidney.

-Only small amount is excreted by the kidney.

- ***Pegylated interferon*** *:* attachment of IFN proteins to large, inert polyethylene glycol molecules (pegylation) slows the absorption, decreases the clearance, and provides higher and more prolonged serum concentrations that enable once-weekly dosing.

- Two pegylated interferons are available commercially: *peg-interferon alpha-2a* and *peg-interferon alpha-2b*.

Uses of pegylated interferon alpha:

1-Its role in treating hepatitis B and C is limited now (mainly for HBV e positive Ag).
2- As adjunctive treatment in certain tumors as non-Hodgkin's lymphoma, hairy cell leukemia, , multiple myeloma, and AIDS-related Kaposi sarcoma.
3-It is used in treating Genital warts (condyloma accuminata) caused by Human papilloma virus; and in severe cytomegaloviral and herpes zoster infections..

Adverse effects:

a) Influenza-like illness (fever, chills, headache, myalgia, nausea and vomiting).
b) Bone marrow depression.
c) CNS: confusion, **seizures** and behavioral changes.
d) Renal toxicity and cardiac toxicity.
e) With chronic use: anorexia, fatigue, weight loss, development of antibodies that decrease the antiviral activity.
f) Retinopathy, hearing loss and pneumonitis.

It is contraindicated in cardiac patients and during pregnancy

Direct acting anti-HCV drugs (DAA)

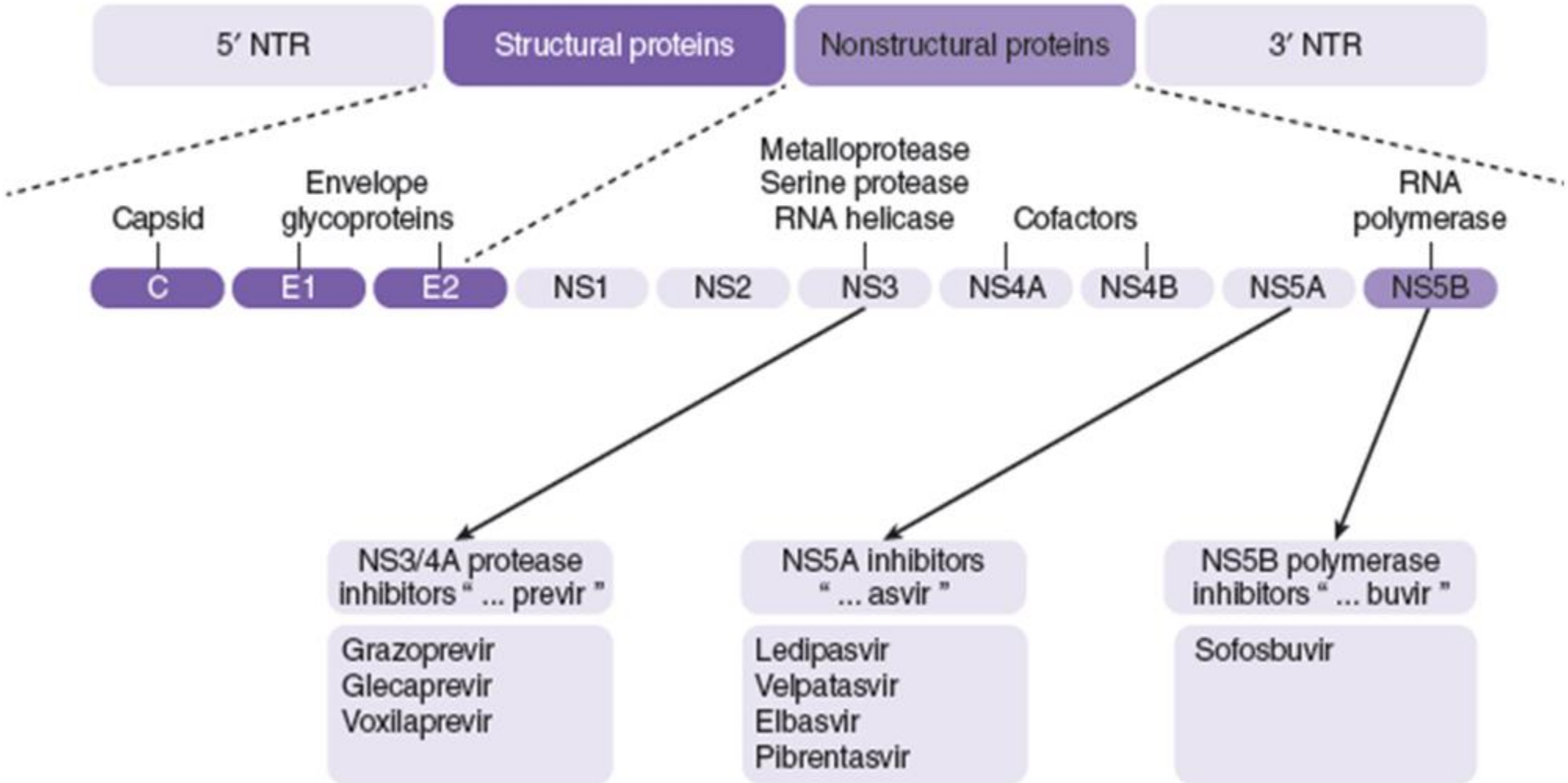
- Target specific nonstructural (NS) viral proteins that play role in replication of HCV inside hepatocytes.
- Less efficacy & development of resistance on using as monotherapy
- Used in combination therapy against HCV
  - Shortens duration of therapy
  - Improves clinical response.
- Minimal ADRs
- Significant drug interactions

➢ Until 2011, a combination of pegylated interferon and ribavirin was the standard treatment for patients with HCV

There are four current classes of DAAs, which are defined by their mechanism of action and therapeutic target:

1- nonstructural protein (NS)5A inhibitors
2- NS5B nucleoside polymerase inhibitors,
3-NS5B non-nucleoside polymerase inhibitors (none available currently)
4- NS 3/4A protease inhibitors

The choice of treatment regimen is determined by several factors, including HCV genotype, HIV &/or HBV co-infection, the presence of renal insufficiency, treatment history, and the presence of cirrhosis.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Structural proteins
Nonstructural proteins
3′ NTR
Capsid
Envelope glycoproteins
Metalloprotease
Serine protease
RNA helicase
Cofactors
RNA polymerase
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NS3/4A protease inhibitors " ... previr "
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Voxilaprevir
NS5A inhibitors " ... asvir "
Ledipasvir
Velpatasvir
Elbasvir
Pibrentasvir
NS5B polymerase inhibitors " ... buvir "
Sofosbuvir

Sofosbuvir

Mechanism of action:

-Sofosbuvir is a pro-drug & converted to triphosphate active form, which inhibits HCV RNA polymerase, resulting in inhibition of RNA synthesis.

✓ Little resistance develop to sofosbuvir.

Pharmacokinetics

-Sofosbuvir is used only **orally**.

-T ½ of sofosbuvir is 0.4 hour, but its metabolite has t1/2 = 27 hours (once daily dose).

Therapeutic uses

❑Sofosbuvir is used in combination with other oral direct acting antiviral drugs for **treatments for HCV.**

✓ **Sofosbuvir** in combination with velpatasvir is recommended for **all genotypes** with a cure rate greater than 90%. The duration of treatment is typically 12 weeks.

- ❑ for HCV genotypes 1, 4, 5, and 6 (**sofosbuvir** with ledipasvir).
- ❑ For HCV genotype 2 and 3 (**sofosbuvir** with **ribavirin**).
- ❑ For HCV with **cirrhosis or liver transplant patients**, **ribavirin** is sometimes added.
- ➢ Peg-interferon with or without sofosbuvir is no longer recommended in an initial HCV treatment.
- ➢ Compared to previous treatments; sofosbuvir-based regimens provide a higher cure rate, fewer side effects, and a two- to four-fold reduced duration of therapy.

Side effects of sofosobuvir

- **Fatigue**, headache, nausea, rash, irritability, dizziness, **back pain,** and anaemia are the common side effects .
- -Sofosbuvir may reactivate hepatitis B in previously infected patients.
- Safety during pregnancy is unclear; some of the medications used in combination may result in harm to the baby.
- Bradycardia when given with **amiodarone** , or beta blockers

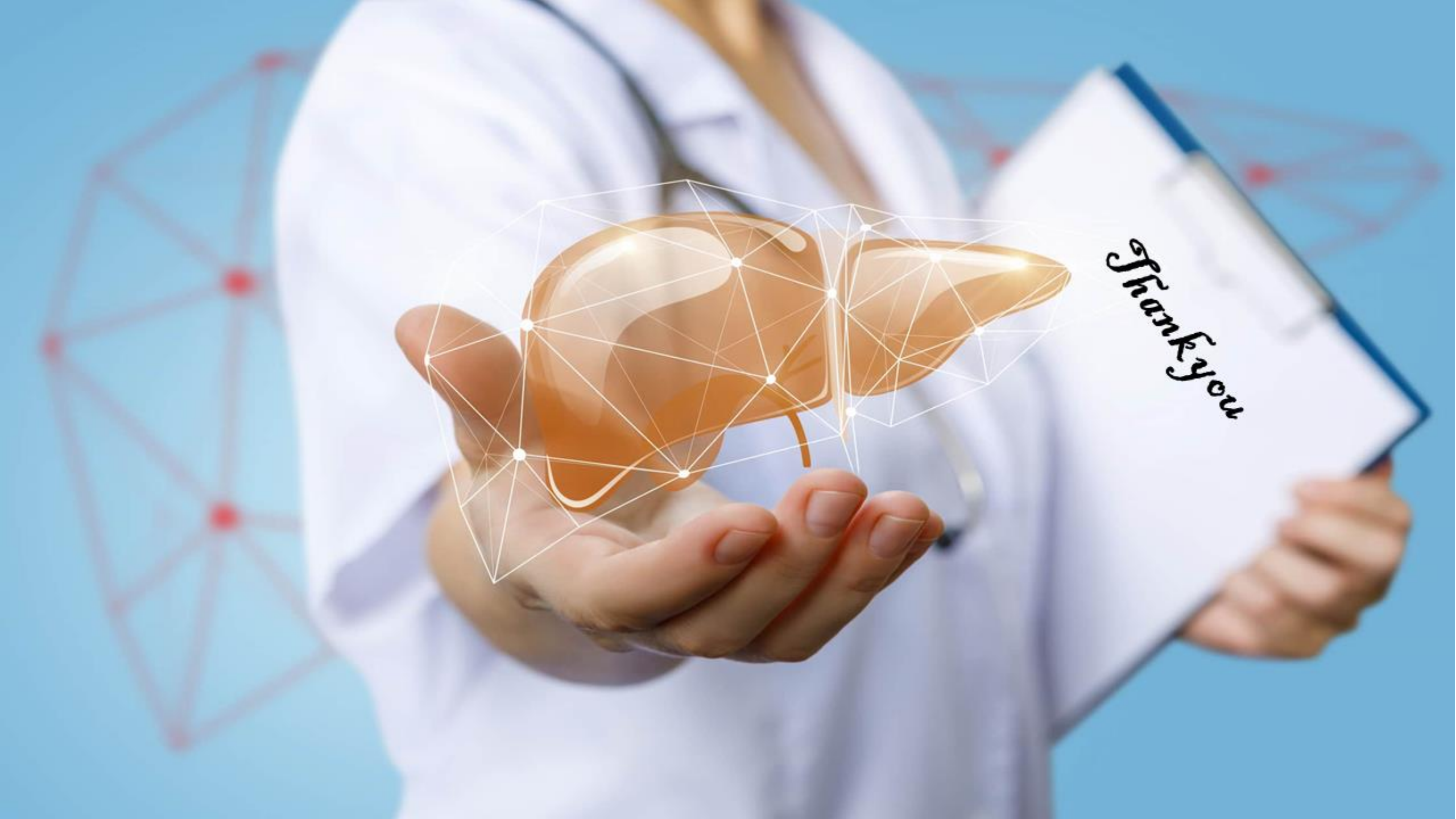
Drug interactions of DAA drugs

- All are metabolised by CYP3A
- All are substrates of P-gp efflux transporter

CYP3A inducers/ inhibitors decrease their effect/increase their toxicity

Inducers of P-gp (Phenytoin/rifampicin) decrease their blood levels

N.B. Velpatasvir need gastric acid for absorption. Their efficacy decreased by H2 blockers


Thankyou