DRUGS USED FOR HEPATITS

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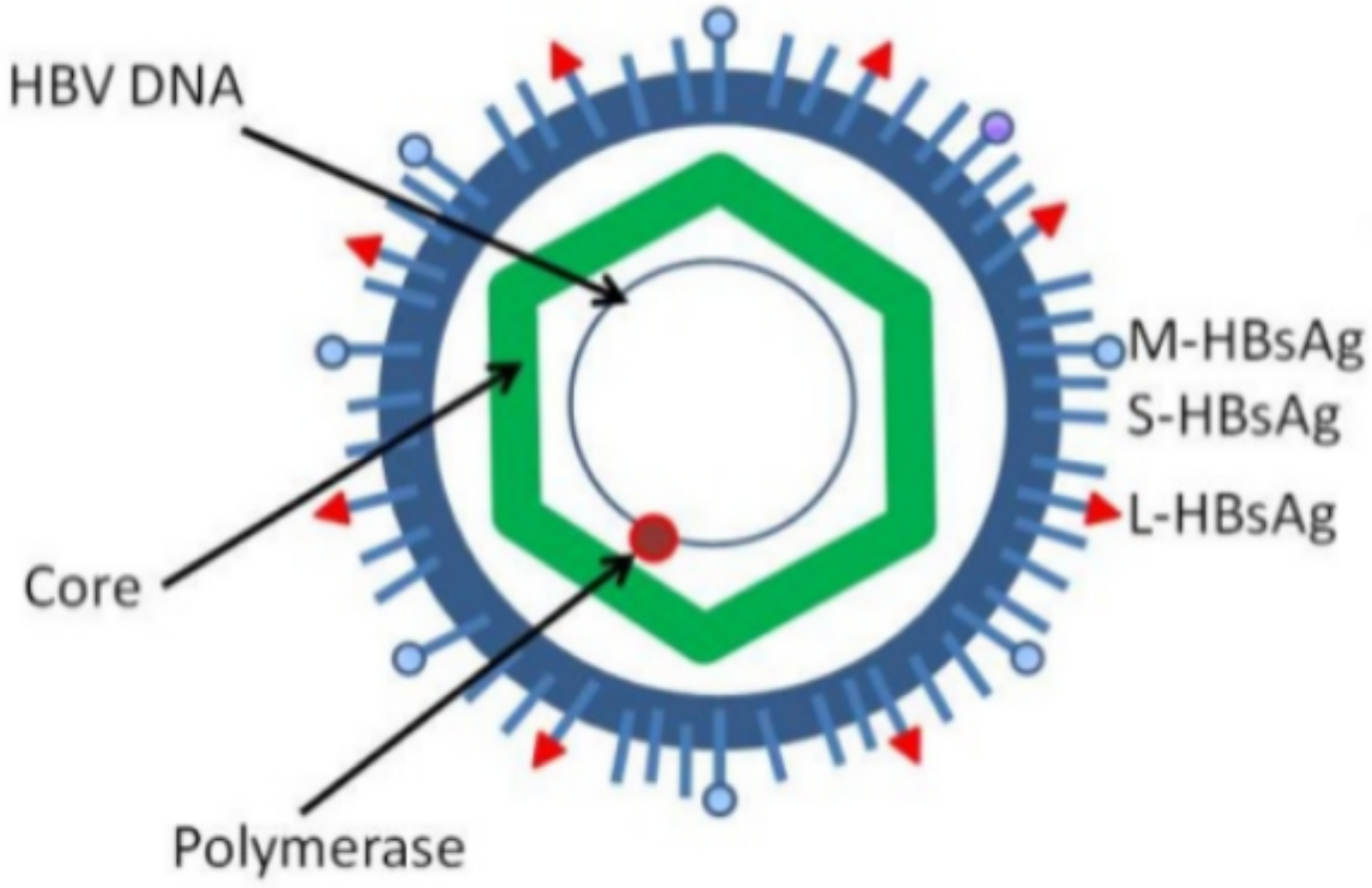
Hepatitis B

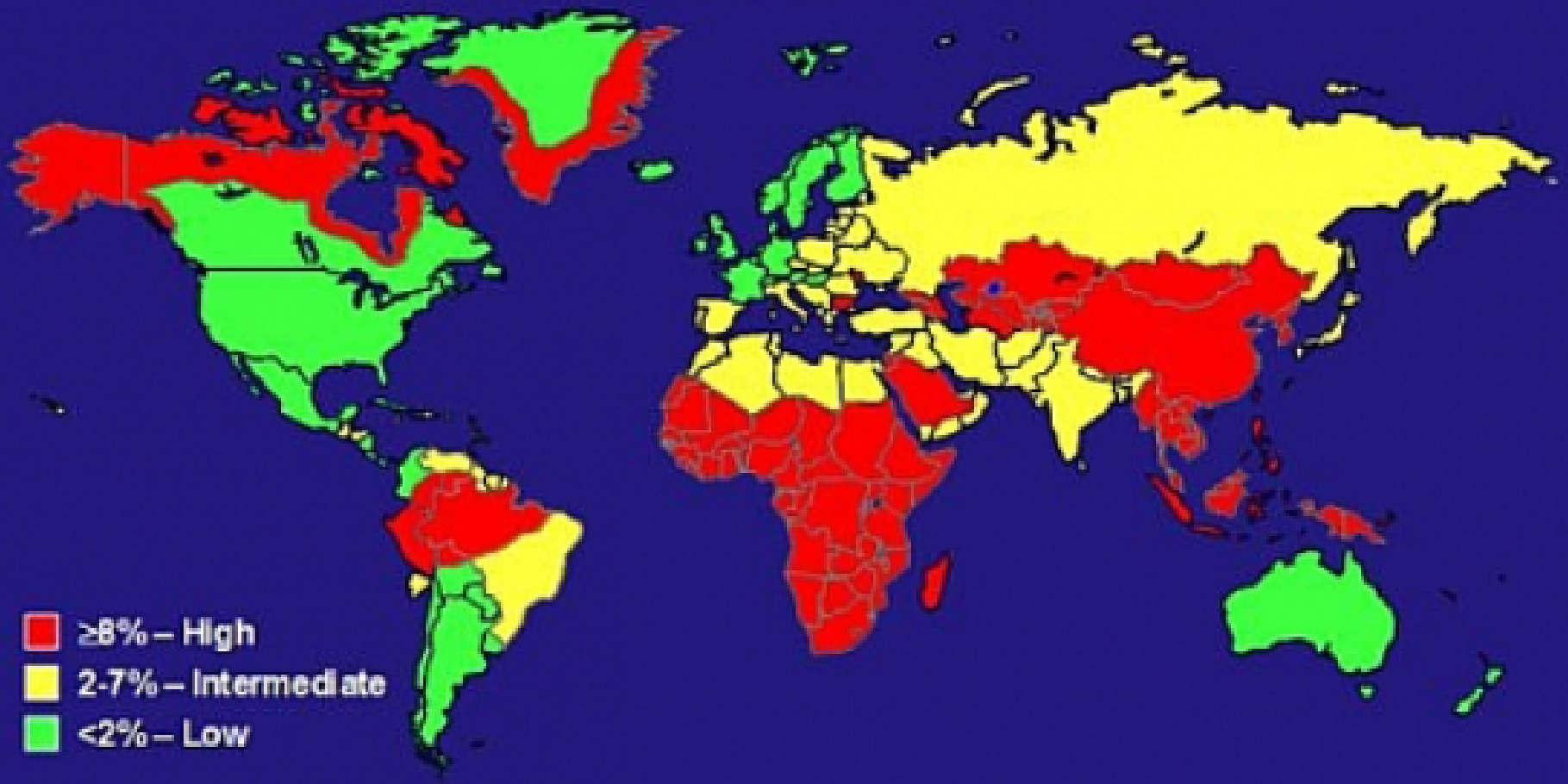
- Hepatitis B is an infectious disease caused by the ***Hepatitis B virus (HBV).***
- It is a major public health problem, causing chronic hepatitis, cirrhosis of liver and hepatocellular carcinoma.
- Around 350 million people are infected worldwide (0.3%), 75% of which are Asians.
- ***Human carcinogen***—cause of up to 80% of hepatocellular carcinomas.

Hepatitis B Virus

- Hepatitis B virus is a member of the ***Hepadnavirus Family***.
- The virus particle, called ***Dane particle (virion)***, consists of an outer lipid envelope and anicosahedral nucleocapsid core composed of protein which encloses the viral DNA and a DNA polymerase that has ***reverse transcriptase activity similar to retroviruses.***
- The envelope protein expressed on the outer surface of the virion and on the smaller spherical and tubular structures is referred to as ***hepatitis B surface antigen (HBsAg).***


HBV DNA
M-HBsAg
S-HBsAg
L-HBsAg
Core
Polymerase

Geographic prevalence of chronic hepatitis B



World Health Organisation. Geographical Prevalence of HBsAg. Data 1996 (unpublished)
http://www.who.int/vaccines-surveillance/graphics/htmls/hepbprev.htm

Management of CHB

- The currently approved treatment options include ***immunomodulatory therapies (including conventional interferon alpha IFNα, Pegylated Interferon α)*** and ***Nucleoside/Nucleotide Analogs (NA's).***
- The nucleoside analogs include (***lamivudine, entecavir, telbivudine and emtricitabine***) and nucleotide analogs include (***adefovir and tenofovir***).

INTERFERON *(FDA 1991)*

- ***IFN-α was the first approved therapy for chronic hepatitis B,*** no longer used in the treatment of Hepatitis B.
- Dose used was a 16-week course of IFN given subcutaneously at a daily dose of 5 million units, or three times a week at a dose of 10 million units,
- ***Seroconversion from HBeAg to anti-HBe occurred in approximately 20%, and, in early trials, approximately 8% lost HBsAg.***
- Initial trials of ***brief-duration IFN therapy in patients chronic hepatitis B were disappointing,*** *suppressing HBV* replication transiently during therapy but almost never resulting in sustained antiviral responses.

LAMIVUDINE *(FDA 1998)*

- The first of the ***nucleoside analogues*** to be approved, the dideoxynucleoside lamivudine inhibits reverse transcriptase activity of both HIV and HBV and is a potent and effective agent for patients with chronic hepatitis B.
- **DOSE –** 100mg P/O Once daily.
- **DURATION** – Until HBeAg Conversion. Patients should receive a period of consolidation therapy of ≥6 months in Western patients and ≥1 year in Asian patients after HBeAg seroconversion.

LAMIVUDINE – Contd

- Clinical and laboratory side effects of lamivudine are negligible.
- Lamivudine has been shown to be effective in the treatment of patients with decompensated hepatitis B, in some of whom decompensation can be reversed.
- Among patients with cirrhosis or advanced fibrosis, ***lamivudine has been shown to be effective in reducing the risk of progression to hepatic decompensation and, marginally, the risk of HCC.***
- Because of the need for long lamivudine treatment courses, low barrier to resistance, and efficacy inferior to that of later generation anti-virals, lamivudine is ***no longer a first-line treatment for chronic HBV.***

ADEFOVIR *(FDA 2002)*

- It is an orally administered nucleotide analog reverse transcriptase inhibitor (ntRTI).
- **DOSE –** 10mg P/O Once daily.
- A 48-week course of adefovir dipivoxil was shown to achieve histologic improvement (and reduce the progression of fibrosis) and normalization of ALT in just over one-half of patients, HBeAg seroconversion in 12%, HBeAg loss in 23%, and suppression to an undetectable level of HBV DNA in 13–21%, as measured by PCR.

ADEFOVIR – Contd

- The therapeutic effect is lost once the drug is stopped. ***Continued treatment is required to maintain the anti-viral response.***
- Among patients co-infected with HBV and HIV and who have normal CD4+ T cell counts, adefovir dipivoxil is effective in suppressing HBV dramatically.

Adefovir – In Lamivudine Resistance

- ***Adefovir dipivoxil is effective in lamivudine-resistant,*** YMDD-mutant HBV and can be used when such lamivudine-induced variants emerge.

- When lamivudine resistance occurs, adding adefovir (i.e., maintaining lamivudine to preempt the emergence of adefovir resistance) is superior to switching to adefovir.

Adefovir – Adverse Effects

- Adefovir was found to be nephrotoxic at high doses (60-120mg).

- Even at 30 mg/d, creatinine elevations of 0.5 mg/dL occurred in 10% of patients; however, at the HBV-effective dose of 10 mg, such elevations of creatinine are rarely encountered. However creatinine monitoring is advised during treatment.

PEGYLATED INTERFERON *(FDA 2005)*

- ***PEG INTERFERON α2a*** is the only Interferon approved for the treatment of Chronic Hepatitis B
- ***DOSE - 180µg SC weekly * 48 weeks.***

ENTECAVIR *(FDA 2005)*

- Entecavir, an oral cyclopentyl guanosine analogue polymerase inhibitor, appears to be the most potent of the HBV antivirals and is well tolerated.
- Entecavir is also effective against lamivudine-resistant HBV infection.
- ***DOSE – 0.5 – 1mg daily.***
- Entecavir has an excellent clinical profile.

TELBIVUDINE (FDA 2006)

- Telbivudine, a cytosine analogue, is similar in efficacy to entecavir but slightly less potent in suppressing HBV DNA.
- ***SIDE EFFECTS –*** Creatinine Kinase elevations, Peripheral Neuropathy, Lactic Acidosis.
- Telbivudine is neither recommended as first-line therapy nor widely used.

TENOFOVIR (FDA 2008)

- ***Tenofovir disoproxil fumarate, an acyclic nucleotide analogue*** and potent antiretroviral agent used to treat HIV infection, is similar to adefovir but more potent in suppressing HBV DNA and inducing HBeAg responses.
- ***DOSE – 300mg once daily (Cost – Rs.45/- per tablet)***
- Tenofovir has supplanted adefovir both as first-line therapy for chronic hepatitis B and as add-on therapy for lamivudine resistant chronic hepatitis B.
- Frequency of tenofovir administration should be reduced in patients with impaired creatinine clearance.

Hepatitis C

HCV was identified in 1989. nearly 170 million infected worldwide

Half of liver transplants performed worldwide are for cirrhosis secondary to HCV.

RNA virus with 6 genotypes with different prevalence for each genotype world wide

70% north America is genotype 1,, genotype 4 most common in Egypt and middle east.

Frequent mutation may happen in the same person (*quasispecies).*

Transmission: blood>> sexual; 20% w/o clear precipitant.

Incubation: 1–5 mos; mean 6–7 wks

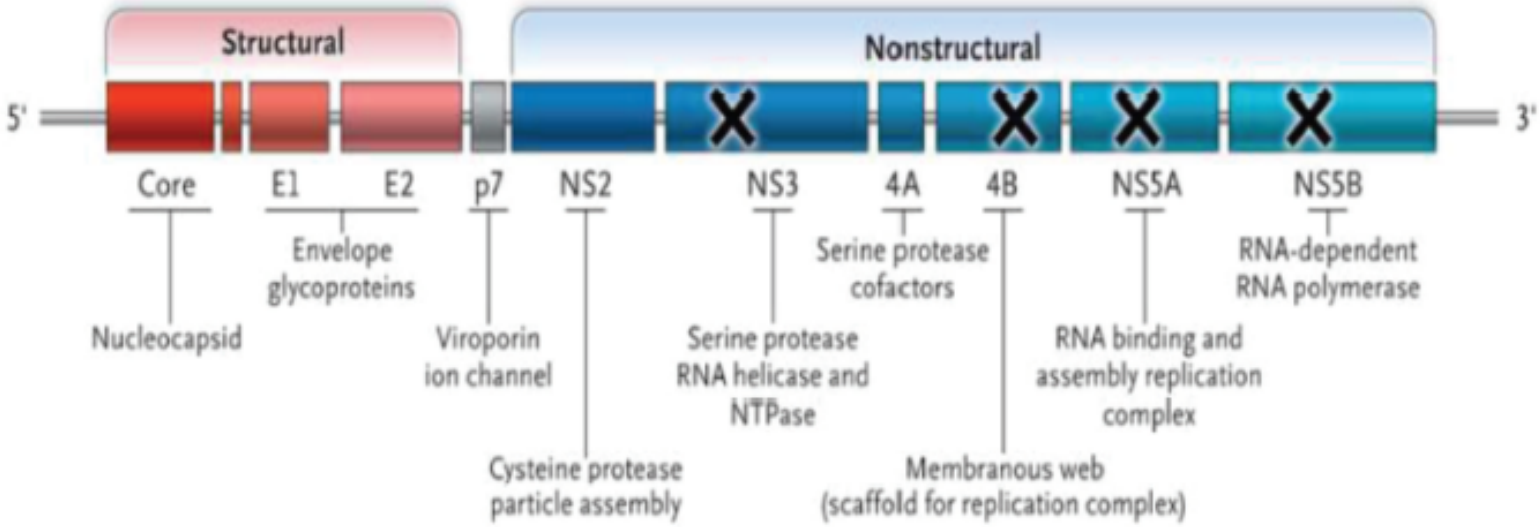
chronic: up to 80% , 20–30% of whom develop cirrhosis (after 20 y)

Serologic and virologic tests:

anti-HCV (ELISA):+ in 6 wks, can be neg. after recovery

HCV RNA: + w/in 2 wks, marker of active infection(gold standerd)

HCV RIBA: used to confirm + anti-HCV ELISA in Pts w/ undetectable HCV RNA



Multiple points of inhibition of hepatitis C virus (HCV) viral replication: Viral replication, a critical part of the HCV life cycle, is mediated by the NS3/4A, NS5A, and NS5B nonstructural proteins. These proteins are currently the main therapeutic targets. Adapted from Lam BP, Jeffers T, Younoszai Z, Fazel Y, Younossi ZM. Ther Adv Gastroenterol 2015;8(5):298–312 .[127]

Therapeutic agents

Ribavirin:

guanosine nucleoside analogue with in vitro antiviral activity against many viruses.

monotherapy has no significant effect on serum HCV RNA

Combined with peginterferon and now with new DAA to reduce relapse

Side effects: dose dependent hemolytic anemia, dose adjustment in renal failure, teratogenicity for both male and female, nausea , pruritic rash

Interferon:

Mainstay of HCV treatment for years, combined with Ribavirin.

2 types: peginterferon alpha 2-a, peginterferon alpha 2-b.

SVR 40% in genotype 1,, while 80% in genotype 2,3

Now used with DAA as a second line therapy, and to shorten the duration of therapy

Relapse rate ~ 20% after discontinuation of interferon based therapy

Side effects: worsening of underlying psychiatric disease

Direct-acting antiviral agents DAA

In contrast to the non-specific antiviral activity of peginterferon and ribavirin, DAAs are designed to inhibit viral proteins involved in the HCV life cycle.

Boceprevir and Telaprevir:

inhibitors of the HCV nonstructural protein 3/4A (NS3/4A) serine protease and the first direct acting antiviral agents to be FDA approved.

Used in combination with rib/interferon regimen enhance SVR.

3 times daily dosing with side effect profile (anemia skin rash)

Simeprevir:

Second generation DAA, NS3/4A protease inhibitor.

Used in combination with rib/interferon for genotype 1

Used in combination with sofosbuvir with minimal side effects

Should not used in decompensated cirrhosis(child b,c)

Sofosbuvir:

Approved in December 2013

Pro drug, its active metabolite acts on NS5B

Used in all genotypes in combination with other DAAs

Renally cleared , not used if GFR less than 30 ml/min

Ledipasvir:

NS5A phosphoprotein inhibitor

Fixed dose in combination with sofosbuvir, approved efficacy for genotype 1

Small studies suggest efficacy for all genotypes, and co-infection with HIV

Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir (OPrD):

Approved in 2014 for genotype 1.

Ombitasvir is an NS5A inhibitor with pangenotypic activity while paritaprevir is an NS3/4A protease inhibitor. Ritonavir is included to inhibit CYP3A activity to increase plasma drug concentration of paritaprevir. Dasabuvir, an NS5B RNA polymerase inhibitor

Combined with ribavirin for genotype 1a (combination not used for genotype 1b).

Not used in pts with decompensated cirrhosis.

Daclatasvir:

NS5A inhibitor

Approved in combination with sofosbuvir for genotype 3 in 2015.

Does not need renal nor hepatic adjustment .

Elbasvir/Grazoprevir:

Grazoprevir is a NS3/4A protease inhibitor while elbasvir is a NS5A inhibitor.

Effective in genotypes 1,2,4,5,6

Used in genotype 1 in pts with ESRD on dialysis

Velpatasvir:

defective substrate for NS5A, higher barrier to resistance than the first generation NS5A inhibitors

combined with sofosbuvir for all genotypes with or without cirrhosis(in combination with ribavirin in decompensated cirrhosis).

Combination (Epclusa) is the **most potent** HCV antiviral medication in the market.

Voxilaprivir:

NS3/4A serine protease ihibitor

available since July 2017 in a fixed dose combination product with Sofosbuvir and Velpatasvir (Vosevi).

use in patients with genotypes 1-6 who have been previously treated with an NS5A inhibitor, or patients with genotypes 1a or 3 infection who have previously been treated with an HCV regimen containing Sofosbuvir without an NS5A inhibitor.

Pibrentasvir:

NS5A inhibitor.

combined with Glecaprevir (Mavyret) since Aug 2017.

Indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both

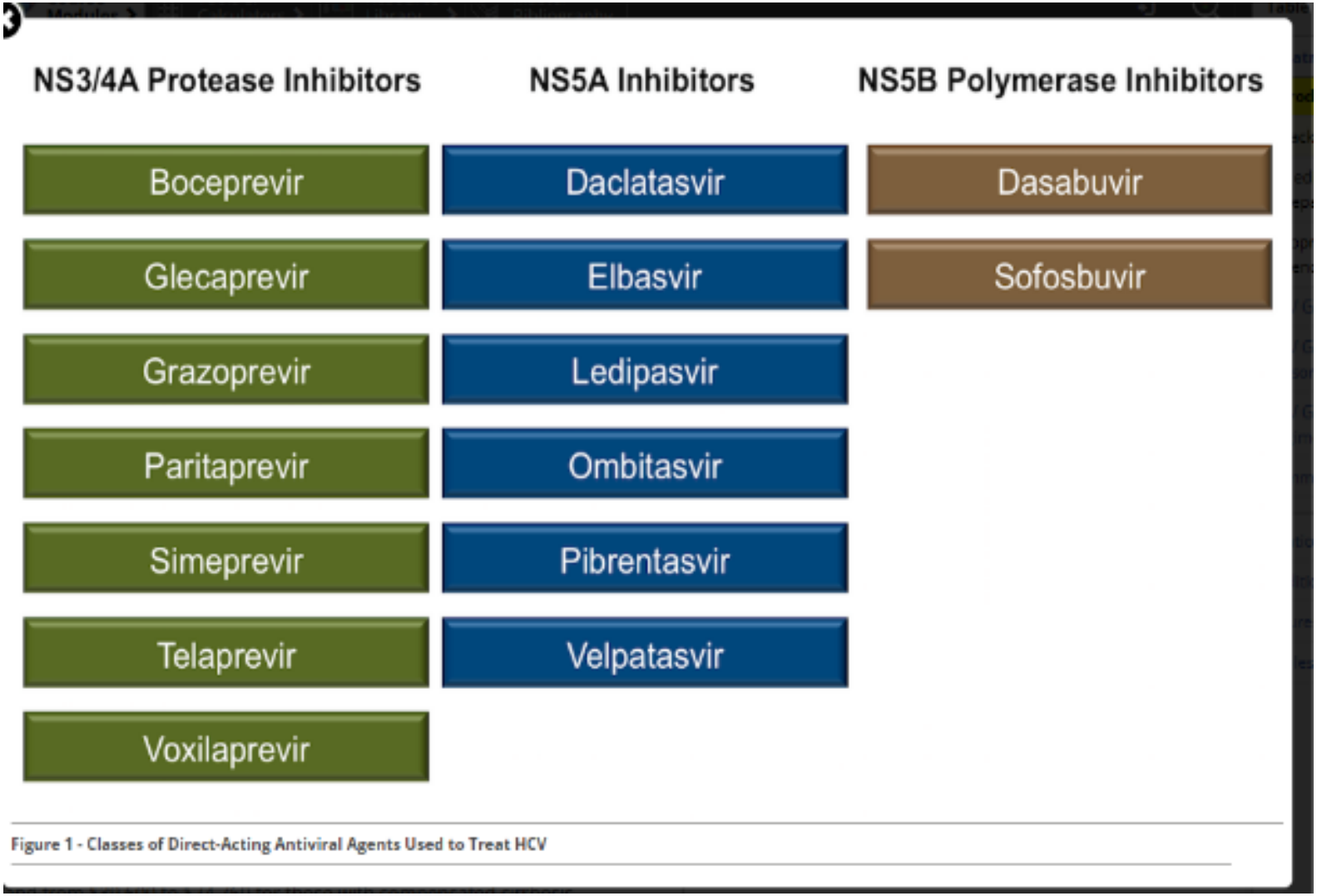


Figure 1 - Classes of Direct-Acting Antiviral Agents Used to Treat HCV

Thank you