Treating Hepatitis C in Patients with Advanced Renal Disease

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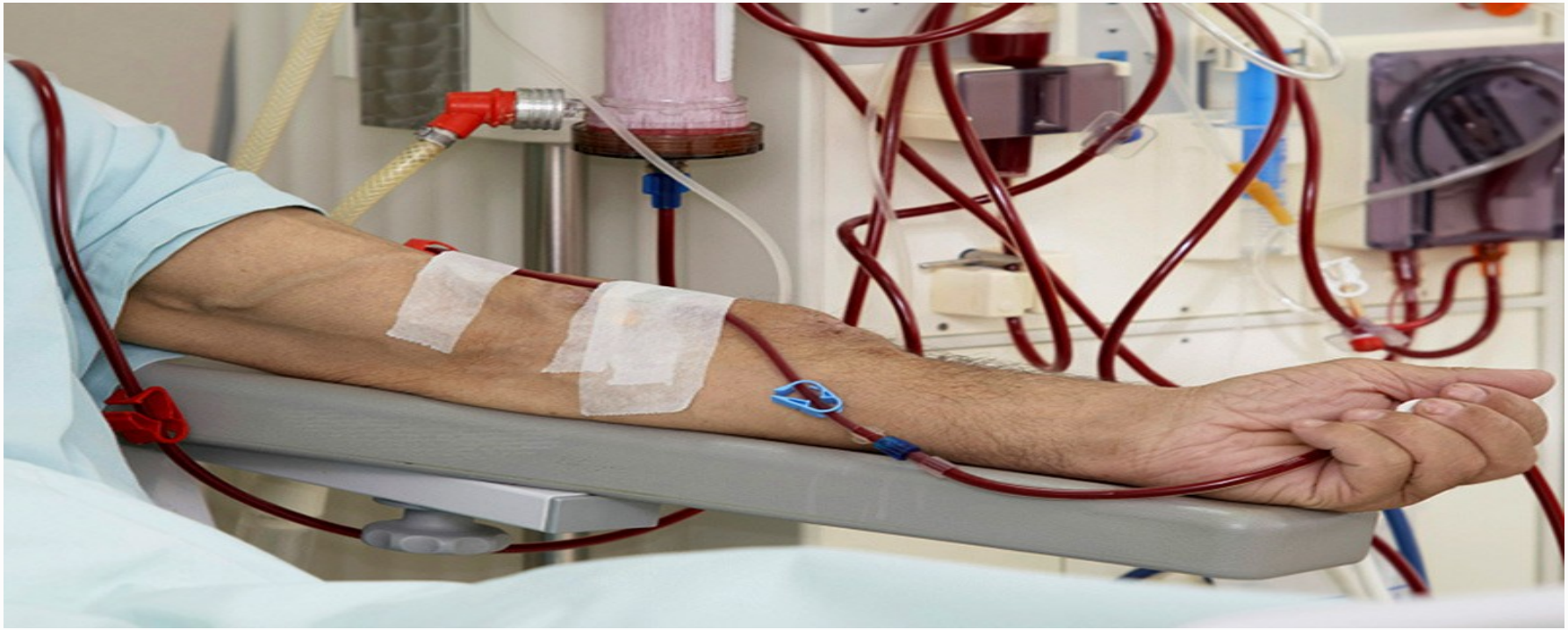
Hemodialysis Patients



Preventive Strategies

- **S**trict adherence to universal infection control precautions seems to be the most important approach to control disease spread in **HD** units.
- **D**esigning and implementation an online network to link the dialysis centers for surveillance system
- **T**herapy of infected patients ASAP
- **H**CV infected should be placed in the priority of renal transplantation but: The clearance of HCV before kidney transplant can probably stop liver damage after transplant and also decrease new-onset diabetes mellitus , HCV–associated glomerulonephritis and transplant glomerulopathy and improve the survival.

Alavian SM. Hepatitis C, Chronic Renal Failure, Control Is Possible! Hepat Mon. 2006

Hemodialysis International 2008; **12**:378–382

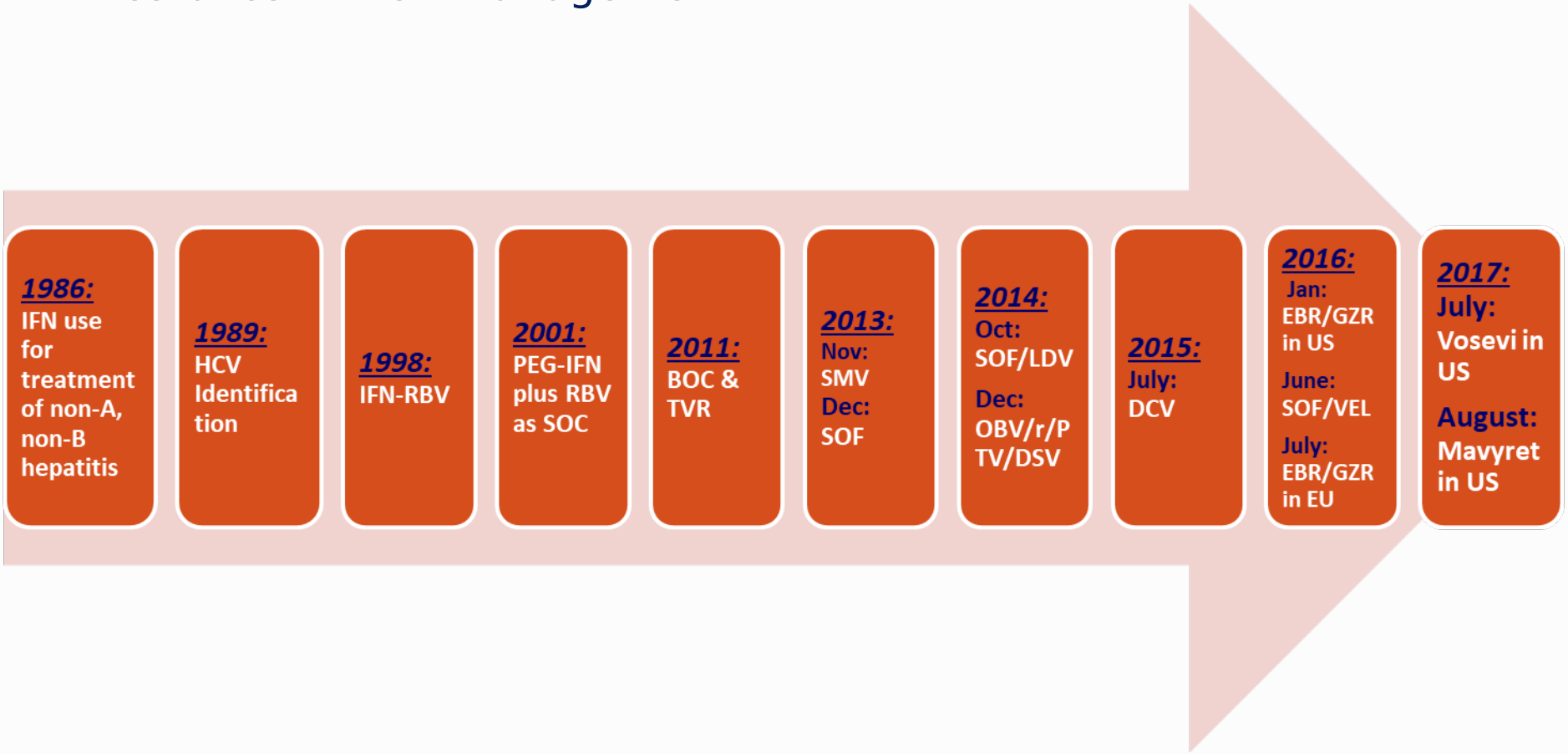
Hepatitis B and C in dialysis units in Iran: Changing the epidemiology

Seyed Moayed ALAVIAN,[1] Kamran BAGHERI-LANKARANI,[2] Mitra MAHDAVI-MAZDEH,[3,4] Shahram NOUROZI[4]

- Prevalence of positive HBS Ag and **HCV Abs** in patients on hemodialysis decreased from 3.8% and **14.4%** in 1999 to **2.6%** and 4.5% in 2006, respectively.

Alavian SM, et al. Hepatitis B and C in dialysis units in Iran: Changing the epidemiology. Hemodial Int. 2008

Milestones in HCV Management



Viable Treatment options for HCV

- **PEG +/- Ribavirin** (really?!) we started the elimination program with these drugs fro at least 15 years
    - Chronic hepatitis c patients with CKD with eGFR>30 ,can be treated with all of the approved DAAs regimens , but for patients with eGFR<30 , we have three approved regimens including:
- Glecaprevir/Pibrentasvir – Mavyret
- Elbasvir/grazoprevir – Zepatier
- Ritonavir-boosted paritaprevir and ombitasvir and dasabuvir

At present, pegylated interferon and ribavirin are considered standard treatment in patients with normal kidney function. In patients with end stage kidney disease, PEG-IFN alfa-2a is generally reduced to 135 μg/week and the weekly dose of PEG-IFN alfa-2b is reduced by 50 % [79••] while ribavirin is generally not prescribed because it is not filtered through hemodialysis filters, accumulates in serum, and causes dose-related hemolysis. Only limited data are available about monotherapy with pegylated interferon and combination therapy (PEG-IFN plus ribavirin) for chronic HCV in the dialysis population. Most studies of patients on he-

Alavian SM, Lankarani KB, Sharara A. Treatment of Chronic HCV in Special Populations: Thalassemia, Hemophilia, and Hemodialysis Patients. Curr Hepat Rep. 2012

Results. Twenty-one studies on IFN-α2a or IFN-α2b (491 patients) and 12 on pegylated-IFN-α2a or PEG-IFN-α2b (279 patients) were evaluated. The pooled SVR for standard and pegylated IFN monotherapy in random effects model was 39.1% (95% confidence interval [CI], 32.1 to 46.1) and 39.3% (95% CI, 26.5 to 52.1), respectively. Pooled dropout rates were 22.6% (95% CI, 10.4 to 34.8) and 29.7% (95% CI, 21.7 to 37.7), respectively. Female

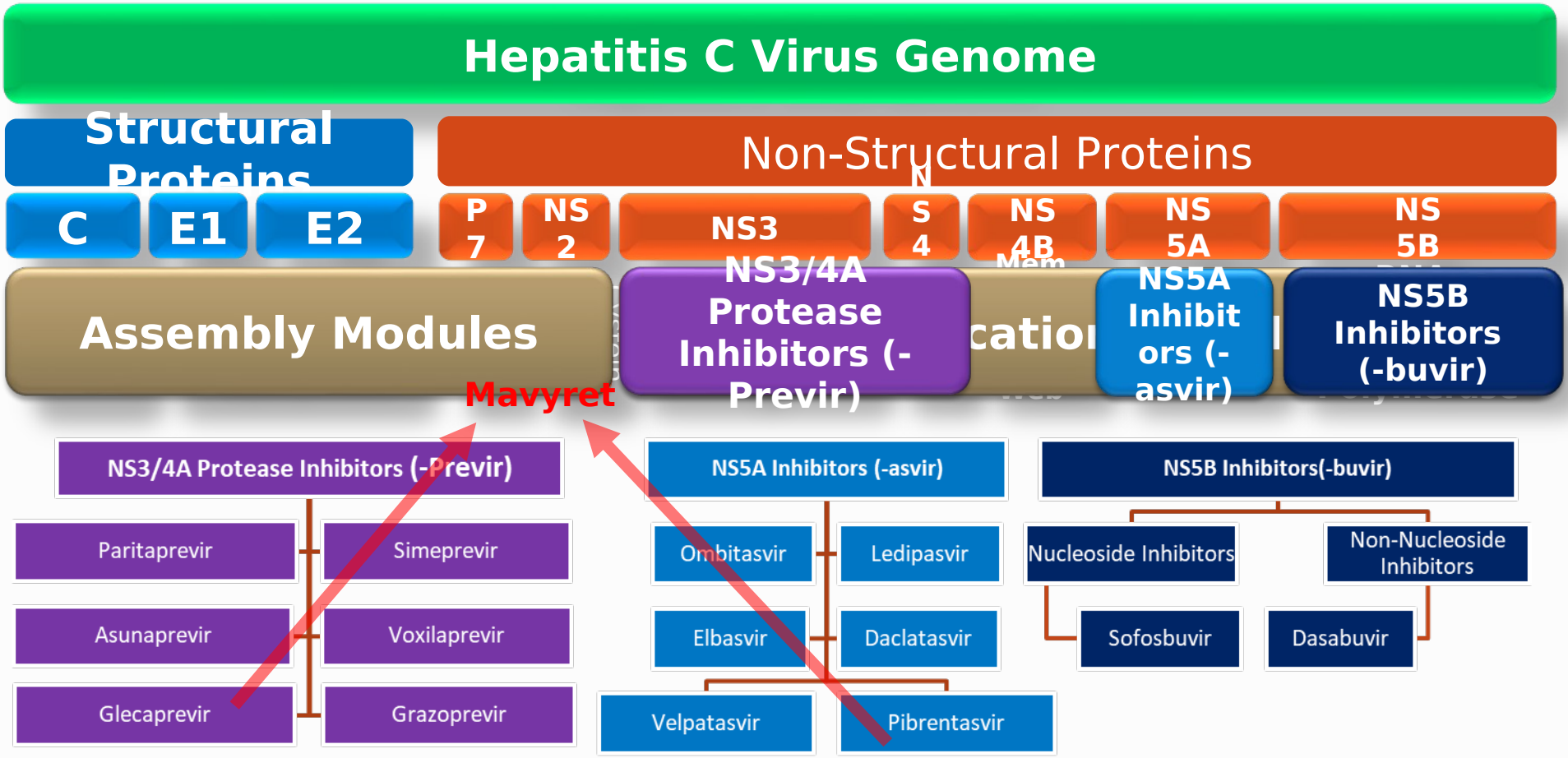
Alavian SM, Tabatabaei SV. Meta-analysis of factors associated with sustained viral response in patients on hemodialysis treated with standard or pegylated interferon for hepatitis C infection. Iran J Kidney Dis. 2010;4

Viable Treatment options for HCV

- PEG +/- Ribavirin (really?!) we started the elimination program with these drugs fro at least 15 years

- **Glecaprevir/Pibrentasvir – Mavyret**
- Elbasvir/grazoprevir – Zepatier
- Ritonavir-boosted paritaprevir and ombitasvir and dasabuvir
- Sofosbuvir based (Sof/Ledi, Sof/Dacla, Sof/Velpa)

HCV Genome and Available Approved Direct Acting Antivirals



Combination of NS5A and NS3/4A Protease Inhibitors

- **To treat HCV genotypes 1-6 without cirrhosis (liver disease) or with mild cirrhosis, including patients with moderate to severe kidney disease**

- **To treat HCV genotype 1 infection, previously treated with a regimen containing an NS5A inhibitor or an NS3/4A protease inhibitor but not both.**
-
- **It is the first treatment of eight weeks duration approved for non-cirrhotic and naïve HCV-Infected Patients with all genotypes**

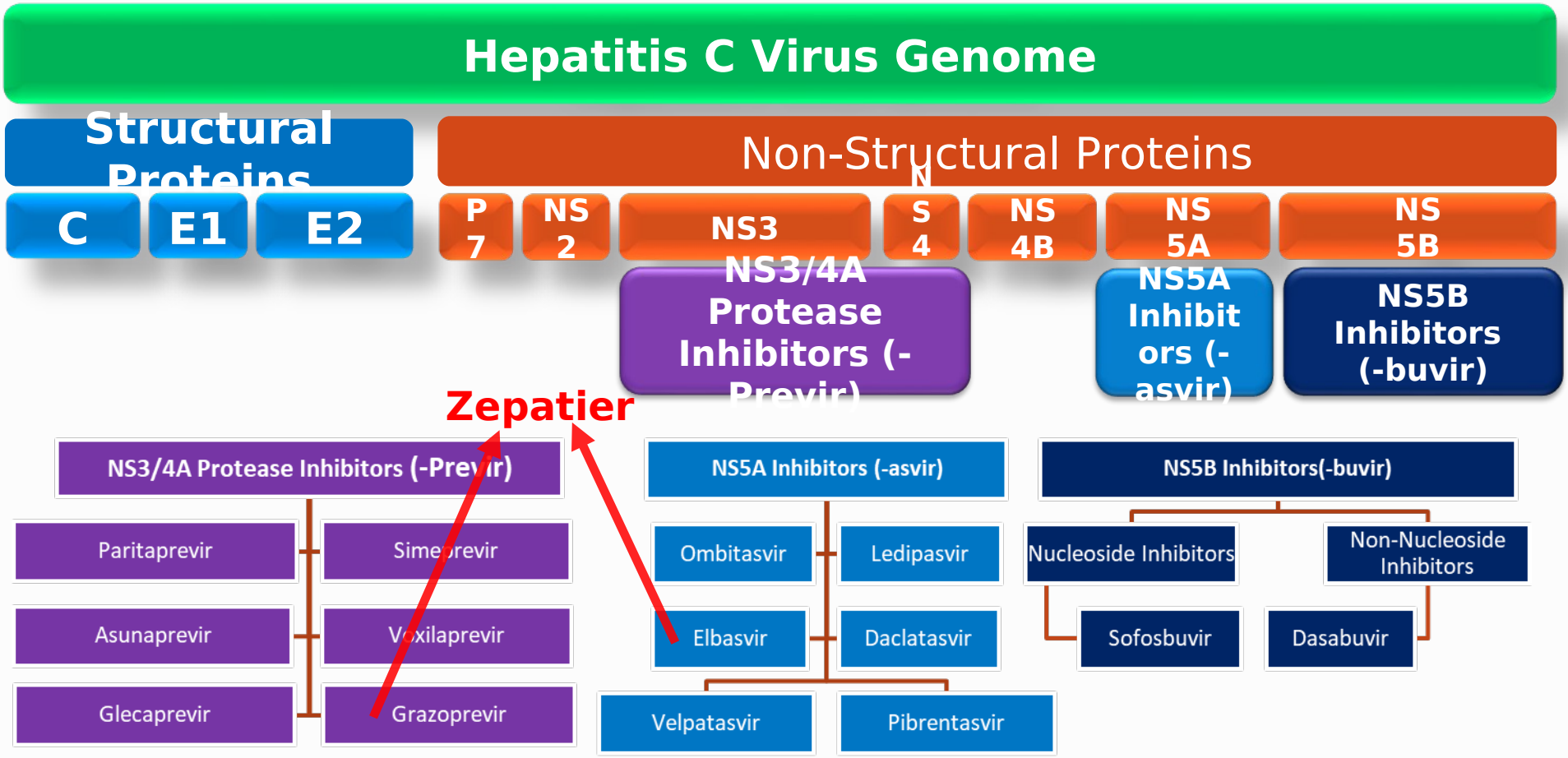
- **The most common adverse : headache, fatigue and nausea.**

- **It is not recommended in patients with moderate cirrhosis and contraindicated in patients with severe cirrhosis of those taking the drugs Atazanavir and rifampin.**

Glecaprevir/ Pibrentasvir – Mavyret

- Glecaprevir/pibrentasvir have been shown to be effective and safe in persons with chronic kidney disease and HCV infection with all six major HCV genotypes.
- Not recommended for Child C (or even B)
- Not available in Iran

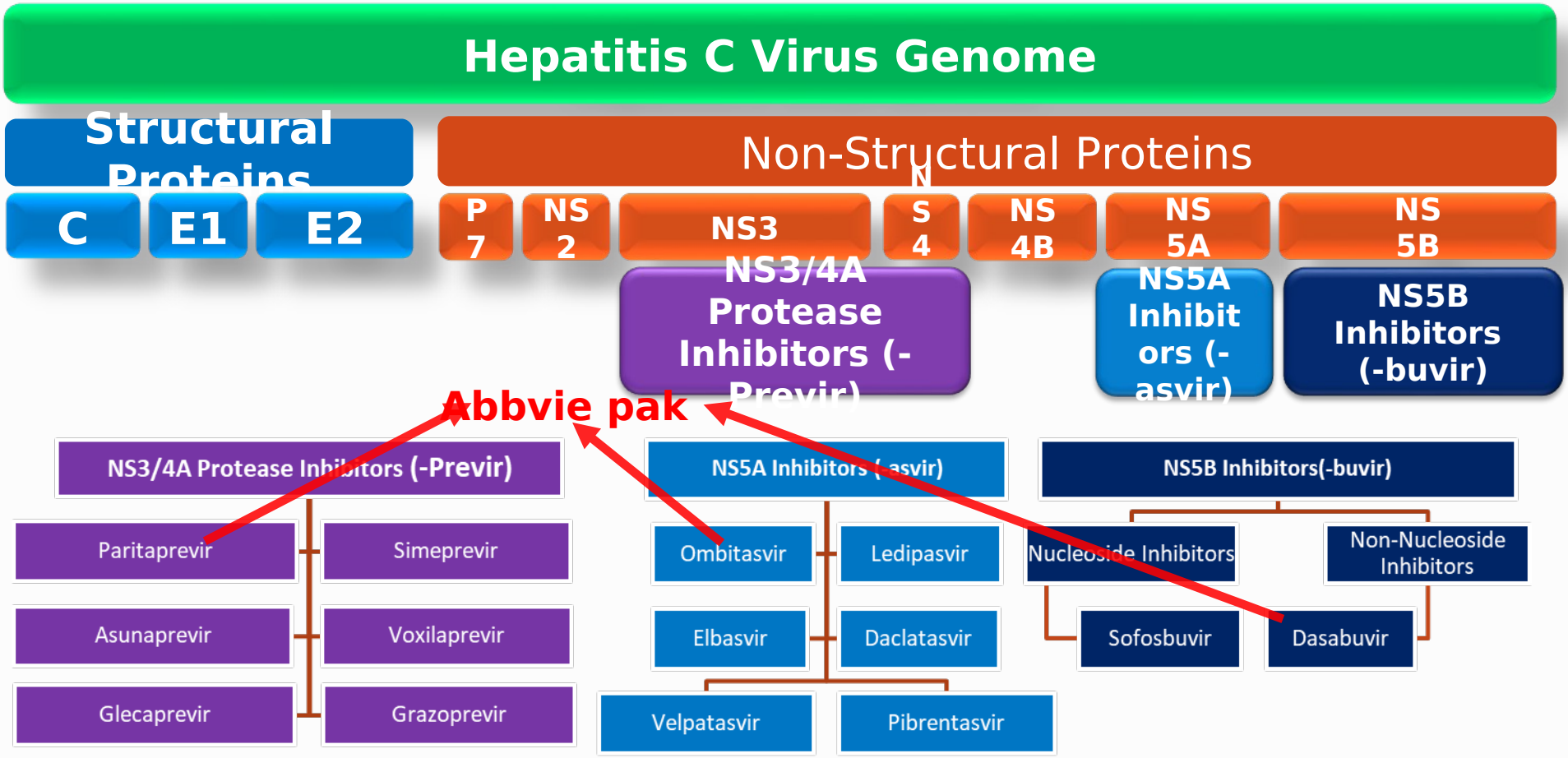
HCV Genome and Available Approved Direct Acting Antivirals



Elbasvir/grazoprevir

- **Safe in renal failure**
- For genotypes 1 and 4
- Not recommended for Child C (or even B)
- Not available in Iran

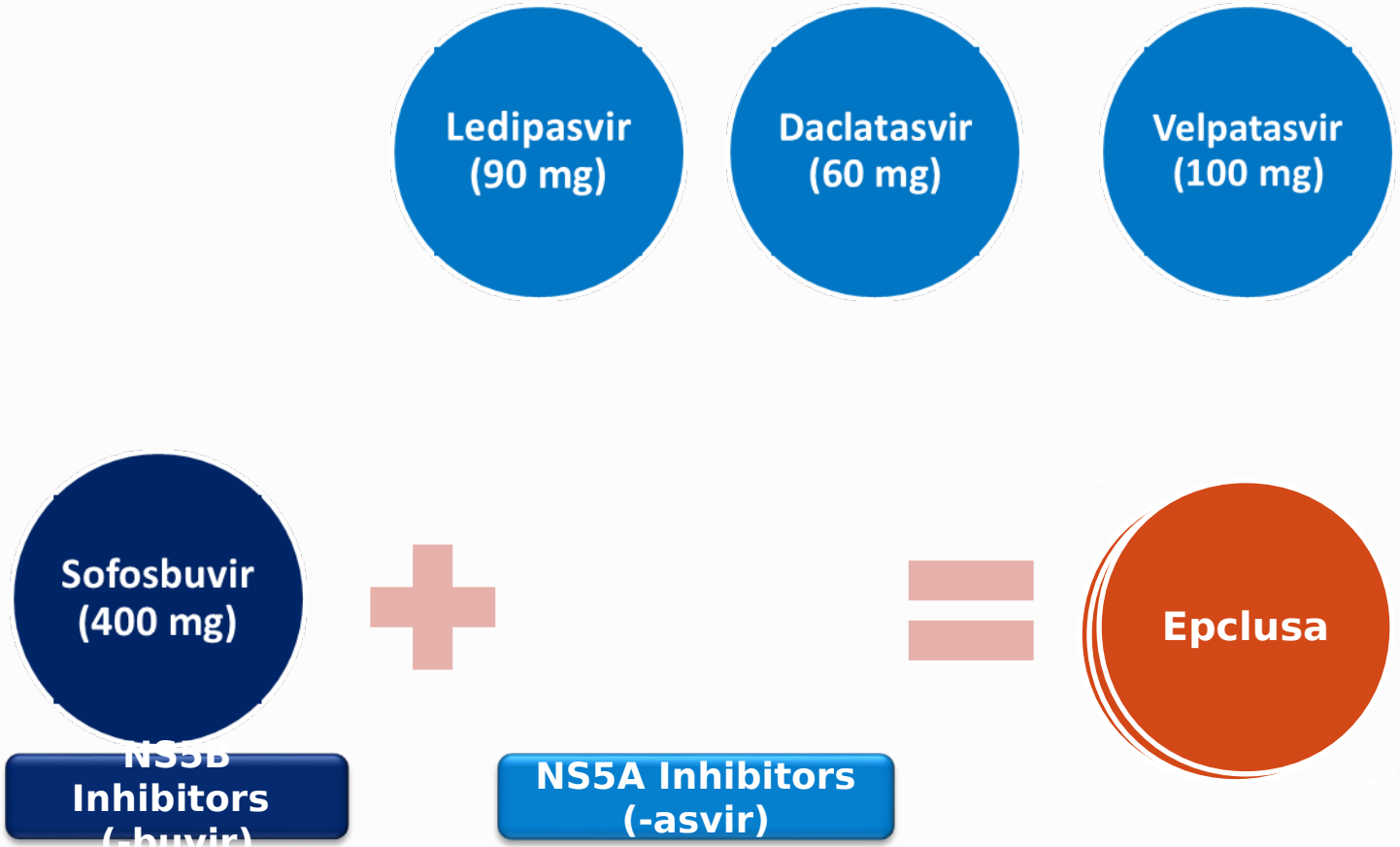
HCV Genome and Available Approved Direct Acting Antivirals



Ombitasvir/paritaprevir/ritonavir±Dasabuvir

- **Safe in renal failure**
- OMV/PTV-r+DSV for genotypes 1
- OMV/PTV-r for genotypes 4
- Not recommended for Child B and C
- Not available in Iran

Combination of NS5B and NS5A Inhibitors



Sofosbuvir based

- Sofosbuvir + ledipasvir/daclatasvir/velpatasvir
- All available in Iran
- Sof-Ledipasvir for G1,4,5,6
- Sof-Daclatasvir/Velpatasvir for all genotypes
- **Ledipasvir/Daclatasvir/Velpatasvir are safe in CRF**: not eliminated by kidneys and so, they can be given even in sever CKD(eGFR<30ml/min) or in hemodialysis patients without dose adjusment.
- Sofosbuvir safe if eGFR > 30 ml/min/1.73 m2

For eGFR <30

- No data on safety of sofosbuvir
- Sofosbuvir itself is not renally excreted but its metabolite, GS331007, is renally excreted and may achieve high levels up to 20x
- No toxicity reported for this metabolite
- Anecdotal case reports and abstracts confirm lack of side effects
- Half-dose sofosbuvir (200mg/d) has been used with poor SVR

SOF/LDV for Pts With Severe Renal Impairment

- Single-arm, open-label phase II study

- Pharmacokinetics
  - Mean SOF, GS-331007, LDV exposures 103%, 501%, 57% higher in study population vs those in the phase II/III SOF/LDV trial populations
- Safety
  - No treatment-related serious AEs or cardiac AEs, discontinuations for AEs, clinically meaningful eGFR change

Lawitz E, et al. AASLD 2017. Abstract 1587.

Efficacy and safety of direct-acting antivirals-based antiviral therapies for hepatitis C virus patients with stage 4-5 chronic kidney disease: a meta-analysis.

- Eleven studies, comprising a total of 264 patients were included for meta-analysis. The pooled SVR12 rate were 93.2%, **89.4%** and 94.7% in total population, patients with sofosbuvir-based therapies and patients with non-sofosbuvir-based therapies respectively.
- For HCV genotype 1 patients, the pooled SVR12 rate was 93.1%.
- The pooled incidence of SAEs was **12.1%** .The pooled discontinuation rate because of AEs or SAEs in our meta-analysis was **2.2%** .

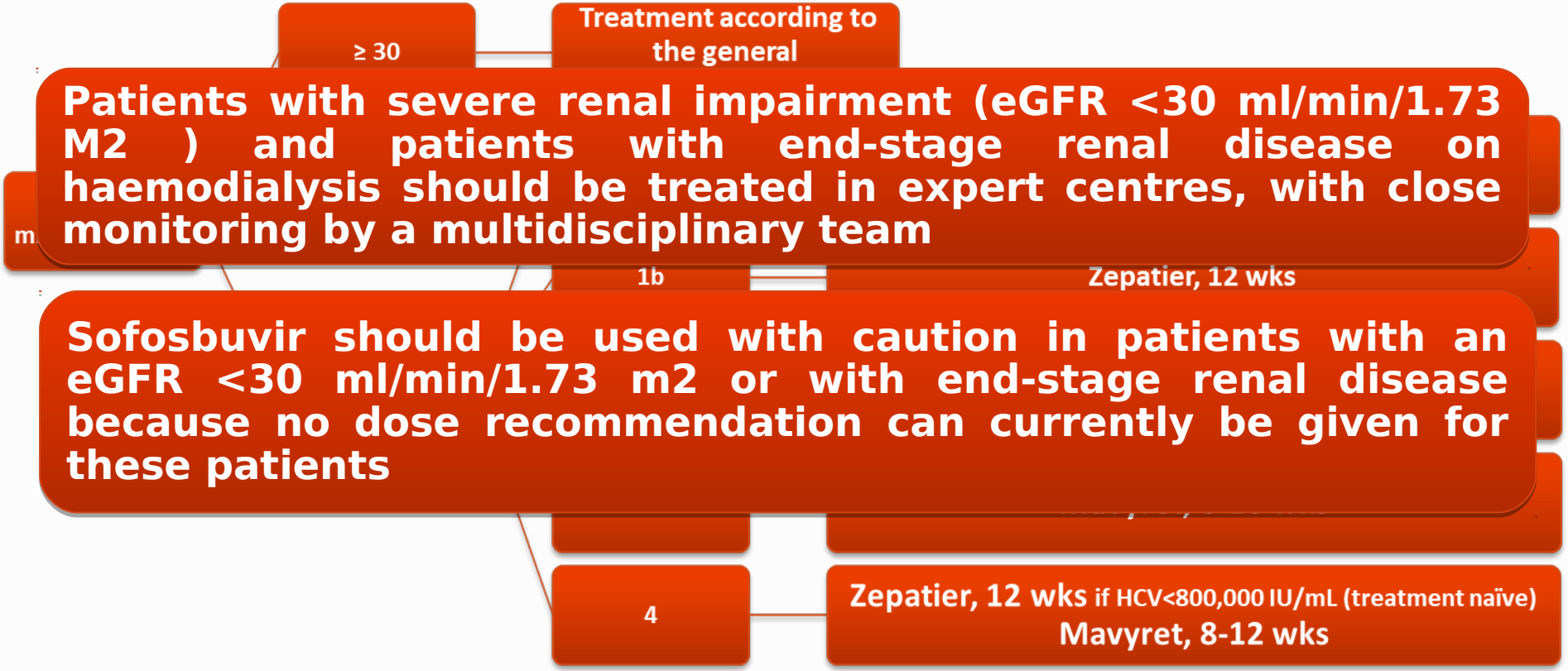
Li T, et al. Efficacy and safety of direct-acting antivirals-based antiviral therapies for hepatitis C virus patients with stage 4-5 chronic kidney disease: a meta-analysis. Liver Int. 2017

Experience in Iran

- **Shariati experiences:** enrolled subjects with severely impaired renal function (eGFR<30) infected with hepatitis C from 13 centers.
- Patients were treated for 12 wks with Sovodak (sofosbuvir 400 mg, daclatasvir 60 mg), 24 wks if cirrhosis
- 74 patients finished treatment
  - 73% on hemodialysis, 42% cirrhosis 7 of which were decompensated
- 3 patients died due to non-treatment related causes
- In the other 71 patients SVR was 100%
- Only side effect observed was diarrhea in one patient

- **MELD Center Experience**: 48 cases with 12 patients cirrhosis on Sof-Dac, just one case stopped the drug due to heart failure and 28 from finished patients all have SVR!

Treatment of HCV-Infected Patients With Renal Impairment



Patients with severe renal impairment (eGFR <30 ml/min/1.73 M2) and patients with end-stage renal disease on haemodialysis should be treated in expert centres, with close monitoring by a multidisciplinary team

Sofosbuvir should be used with caution in patients with an eGFR <30 ml/min/1.73 m2 or with end-stage renal disease because no dose recommendation can currently be given for these patients

Elimination of HCV infection in Iran will be in 2030 but in thalassemia and hemophilia and Patients on hemodialysis is possible in 2020!

Solution: Work together