Treatment Failure in Era of DAAs

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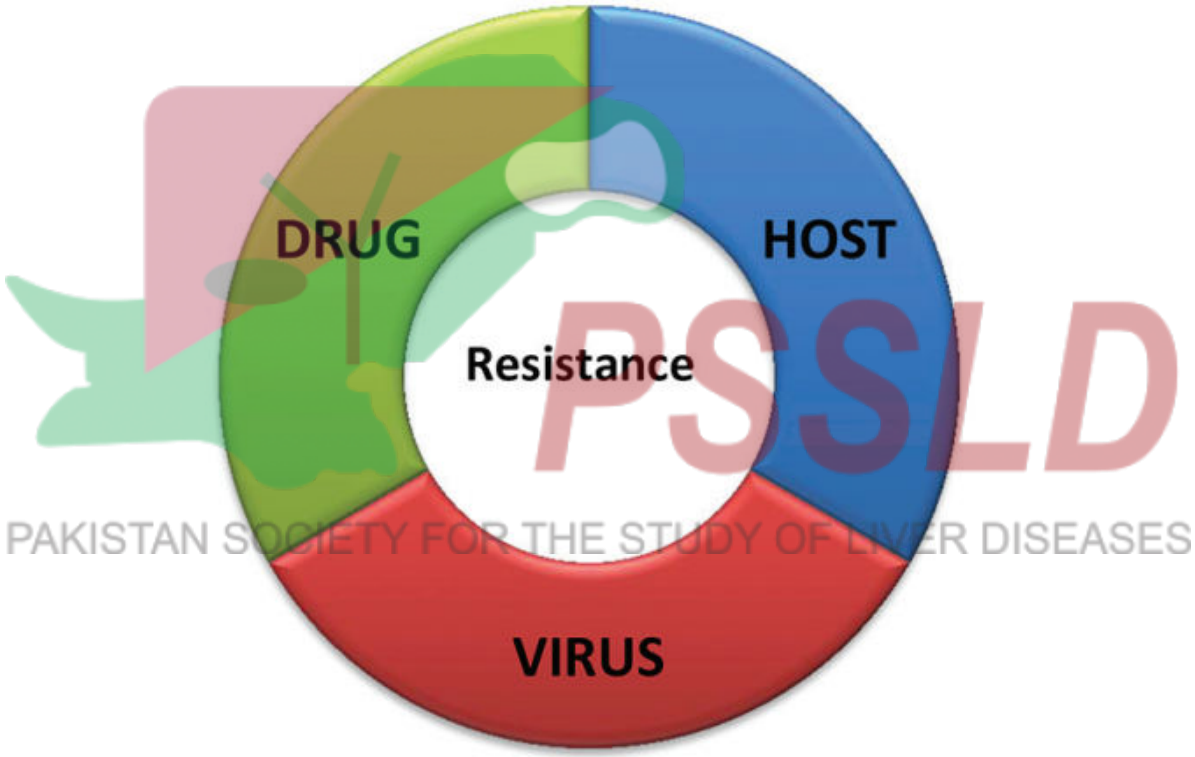
Disclosures

- Nothing to disclose

- A 51 years old male patients who relapsed after 12 weeks treatment of SOF/VEL, presented to the liver clinic
- How would you manage this patient?

- All-oral, once-daily, 8- to 12-week treatment regimens are now standard of care, with viral eradication possible in >95% of patients
- Newer pangenotypic regimens include
  - the NS3/4A protease inhibitor pibrentasvir plus the NS5A inhibitor glecaprevir
  - the NS5B polymerase inhibitor sofosbuvir in combination with the NS5A inhibitor velpatasvir plus the NS3/4A protease inhibitor voxilaprevir
- Despite these advances, several unresolved issues and challenges remain

Factors affecting treatment outcome and development of resistance



Hassany M & Elsharkawy A: In: Advances in Treatment of Hepatitis C and B. Intechopen.com

Virus-related factors

- Genotype
- Baseline resistance associated variants (RAVs) or resistance associated substitutions (RASs)

Drugs-related factors

- Potency and genetic barrier
- Drugs combinations
- Postreatment RASs

Host-related factors

- Non-Adherence to therapy
- HIV, post-organ transplantation and polymedicated patients
- Treatment status: naïve / experienced
- Hepatic fibrosis stage
- Reinfection

Welzel TM et al Gut 2016;65: 1861–1870.

Measures to improve adherence

Recommendations	Grade of evidence	Grade of recommendation
HCV treatment should be delivered within a MDT setting, with experience in HCV assessment and therapy	A	1
HCV-infected patients should be counselled on the importance of adherence for attaining an SVR	A	1
Social support services should be a component of HCV clinical management for patients with socioeconomic disadvantages, migrants	B	1
Peer-based support and patient activation assessment are recommended to improve HCV clinical management	B	2
Patients with harmful alcohol consumption should receive additional support during antiviral therapy	B	1

EASL CPG HCV. J Hepatol 2018;69:461–511.

Genotype 3

- Genotype 3 is associated with
  - Lower response rate
  - increased fibrosis progression
  - higher risk of HCC development

(Probst A, et al. J Viral Hepat 2011;18:745–759)

Fibrosis Assessment

- **Transient elastography**
  - > 12.5 KPa = cirrhosis
- **Serum tests**
  - **FibroTest** (0.75 = cirrhosis)
  - **APRI or FIB-4 –** very attractive, can be done anywhere by any provider
    - Very good **negative predictive value – rule out cirrhosis**
- **Ultrasound –** needed in all patients?
  - Insensitive for cirrhosis – only needed if cirrhotic to exclude HCC before treatment
- **Biopsy** rarely needed

If Cirrhosis is Present

- **Need to exclude current or past decompensation**
  - Affects choice of regimen – No PIs, add RBV
  - Affects safety – warn patient & monitor closely
- **Calculate Child Pugh Score – if > 5 pay attention!**
  - Bilirubin
  - Albumin
  - INR
  - Ascites
  - Hepatic encephalopathy
- **Calculate MELD – if > 18 pay attention!**
  - Bilirubin
  - INR
  - Creatinine

Diagnosis of HCV RASs

- Helps in proper selection of the best DAA drug for retreatment
- **Phenotypic analysis**: used to determine the optimum plasma concentration (effective concentration, EC50 EC90) of the drug sufficient to inhibit the viral replication
- **Genotypic analysis:** (sequence analysis): used to detect the amino acids substitutes which cause drug resistance and treatment failure

Diagnosis of HCV RASs

- NS5A RAS testing is recommended for genotype 3-infected, being considered for 12 weeks of sofosbuvir/velpatasvir
  - treatment-naive patients with cirrhosis
  - treatment-experienced patients (without cirrhosis).
- If Y93H is present, weight-based ribavirin should be added or another recommended regimen should be used

AASLD /IDSA Guidance Nov 2019, www.HCVGuidance.org

- The presence of Y93H in genotype 3 patients decreased the SVR12 to 84% (21/25 patients) compared to 97% (242/249) in those without this RAS (Foster GR et, al, NEJM 2015;373:2608-17). lower relapse rates in GT3 patients with cirrhosis receivingribavirin (Esteban, 2018)

Selection of the best DAA drug for retreatment

- **The patients have no RASs**:
  - Retreatment using the same failed regimen (or adding other drugs)
  - Add ribavirin if needed but not previously added
  - Choose the ideal (longer) duration according to the patient status
- **The patient has RASs to protease or polymerase inhibitors**:
  - These will disappear after few weeks or months, so we could choose either to wait until reset point or
  - Use another family of DAAs like NS5A inhibitors plus sofosbuvir

Selection of the best DAA drug for retreatment

- **The patient has RASs to NS5A inhibitor (Drug-Specific RASs)**:
  - Failed drug could not be used but other drugs from the same family could be
- **The patient has RASs to NS5A inhibitor (Drug-Class RASs)**:
  - Class RASs may or may not confer resistance to a specific drug in that class
  - However, changing the whole group to protease inhibitors will be the best way

Glecaprevir /Pibrentasvir for 8 weeks in young Pakistani treatment-naive, non-cirrhotic patients

- GT3 accounts for ~80% of all HCV infections in Pakistan (Virol J 2011;8:433)
- A30K mutation accounts for ~5% to 10% of those with GT3 HCV infection
- Out of 1000 HCV patients, 800 GT3, 40-80 GT3 with A30K
- SVR rate for GT3 with A30K drops from 99% to 75%

- Therefore, out of 1000 patients:
  - Non-GT3 SVR: (99%) =198
  - GT3 without A30K (99%)=733
  - GT3 with A30K (75%)=45
  - Overall SVR without genotyping with BP = 976
- 24 (2.4%) treatment naïve, non-cirrhotic patients will not achieve SVR

HCV NS5A inhibitor experienced patients

- The most prevalent RAS in genotype 3 is Y93H, which is commonly detected following daclatasvir (Julia D, et al. Gastroenterology 2018;154:976–988)
- Most NS5A RASs are known to persist for several months to years after treatment failure and may significantly impact retreatment options (Krishnan P, et al. J Hepatol 2015;62:S220)

SOF/VEL for GT3

- 12 weeks of SOF/VEL is standard of care in patients with HCV GT3
- Addition of ribavirin may still play a roll in
  - patients with cirrhosis
  - baseline Y93H which is associated with decreased velpatasvir activity
- A phase II study of SOF/VEL plus ribavirin for 24 weeks in VEL-experienced patients that yielded an overall SVR of 91% (n = 63/69) (Gane EJ, et al. Hepatology 2017;66:1083–1089)

HCV NS5A inhibitor experienced patients

- In POLARIS-1, patients with HCV (majority with genotype 1 infection) and prior NS5A inhibitor experience received SOF/VEL/VOX for 12 weeks or matching placebo
- Overall SVR rates were
  - 96% (n = 97/101) for HCV genotype 1a
  - 100% (n = 45/45) for genotype 1b
  - 100% (n = 5/5) for genotype 2
  - **95% (n = 74/78) for genotype 3**
  - 91% (n = 20/22) for genotype 4
  - 100% for genotypes 5 and 6 (n = 7/7)
- There were six patients with virologic relapse (four had HCV genotype 3) after the end of treatment

Bourlière M, et al. N Engl J Med 2017;376:2134–2146.

Non-NS5A inhibitor DAA experienced patients (POLARIS-4)

- SOF/VEL/VOX (n = 163) or SOF/VEL (n = 151) for12 weeks
- Overall, 46% of the patients had compensated cirrhosis and most of them had failed previous treatment with SOF
- Response rate: 98% and 90% in SOF/VEL/VOX and SOF/VEL treatment arms, respectively
- Lower SVR in SOF/VEL due to treatment failure among patients with genotypes 1a and 3
- Baseline RASs to NS4/3A and/or NS5A were present in 46% of SOF/VEL/VOX-treated study participants, all of whom achieved SVR

Bourlière M, et al. N Engl J Med 2017;376:2134–2146.

When SOF/VEL/VOX fails

- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin for 16 weeks (Wyles D, et al J Hepatol. 2019;70:1019-23)
- Daily fixed-dose combination of sofosbuvir (400 mg)/ velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin for 24 weeks

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Patients With Prior Glecaprevir/Pibrentasvir Treatment Failure

- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)b plus daily sofosbuvir (400 mg) and weight-based ribavirin for 16 weeks (Wyles, 2019, MAGELLAN-3 trial)
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for 12 weeks. (Pearlman, 2019). For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended

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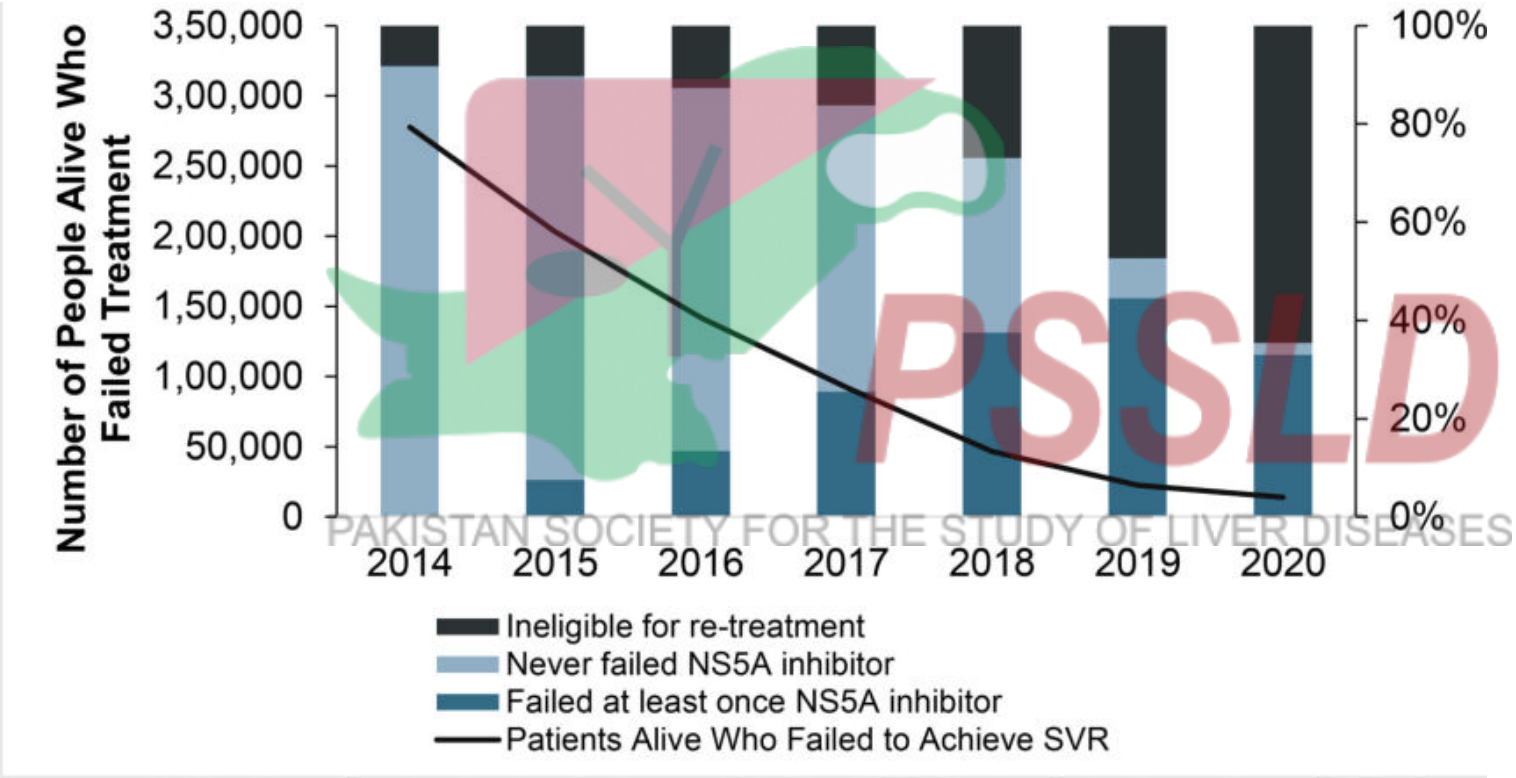
Decompensated cirrhosis

- GLE/PIB and SOF/VEL/VOX both contain an NS3/4A protease inhibitor, are not recommended in patients with decompensated cirrhosis
- SOF/VEL with low initial dose of ribavirin (600 mg; increase as tolerated) for 24 weeks should be considered in a controlled setting
- Ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin for 24 weeks (GT1,4)
- Alternative approach; treat HCV after liver transplantation in transplant-qualified patients (If MELD > 18 or CP-C) with pangenotypic GLE/PIB or SOF/VEL/VOX

Post-treatment follow-up for patients in whom treatment failed

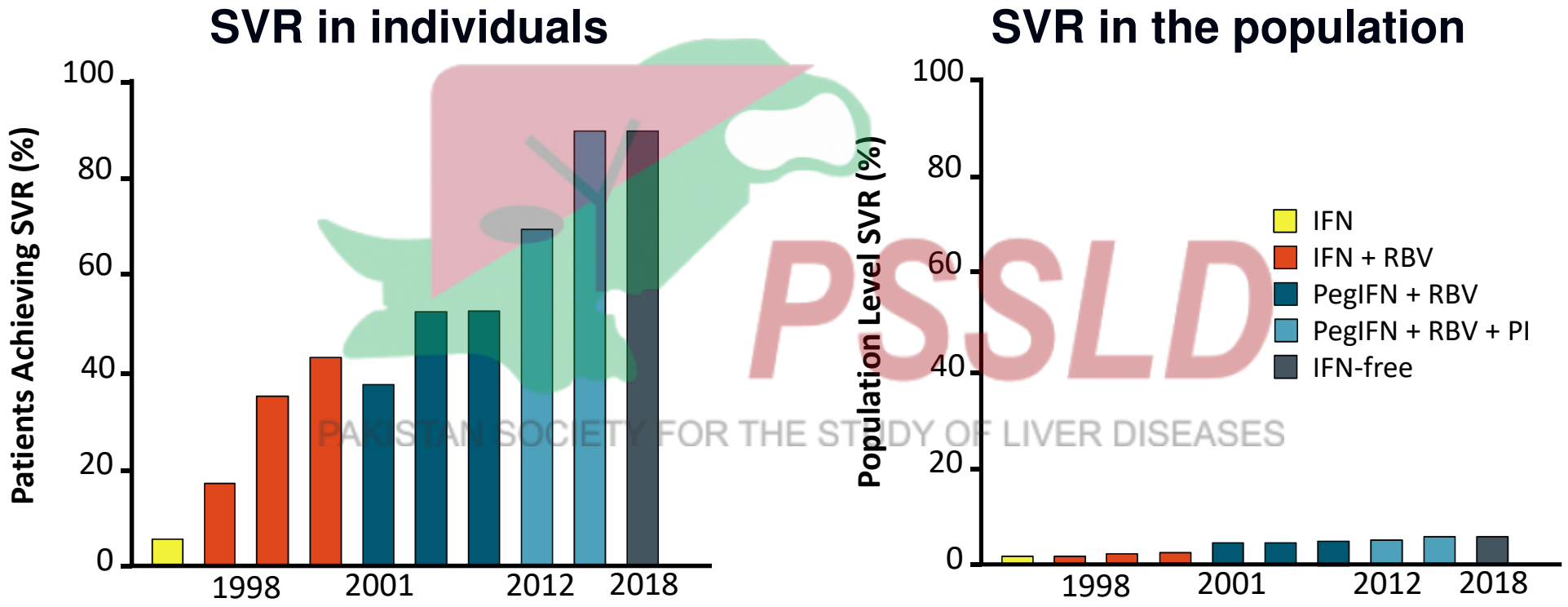
- Disease progression assessment every 6 to 12 months with a hepatic function panel, CBC, INR
- Surveillance for hepatocellular carcinoma with liver ultrasound examination, with or without alpha fetoprotein (AFP), every 6 months for patients with cirrhosis
- Endoscopic surveillance for varices
- Management of decompensated cirrhosis



A. Number of patients alive between 2014 and 2020 who failed to achieve SVR after one or more treatments

Chhatwal J, et al. Aliment Pharmacol Ther. 2018; 47: 1023-1031

HCV Elimination Requires More Than Good Drugs



Grebely. JID. 2013;207(S1):S19.

PAKISTAN SOCIETY FOR THE STUDY OF LIVER DISEASES

Cento V et al. Vironet-C Italian Study

Digestive Liver Dis 2017;49 (Issue 1 Suppl):e8

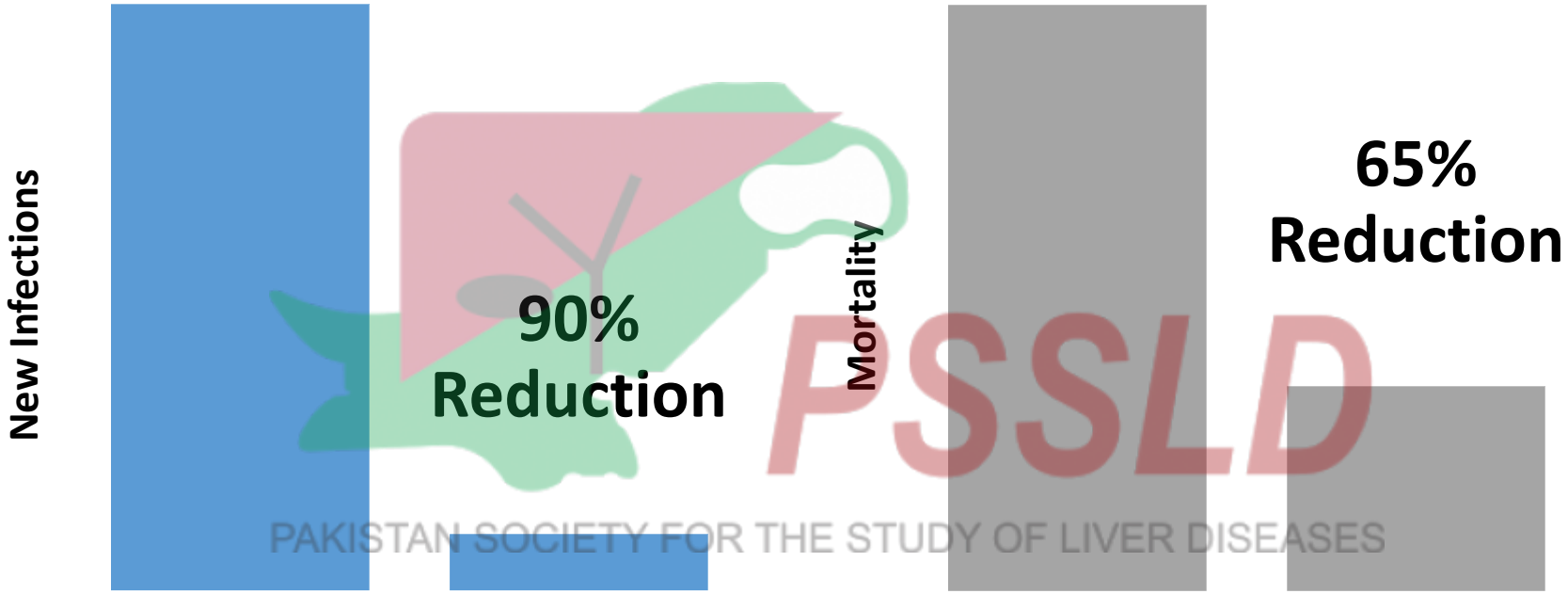
- Real-life retreatment of DAA failing patients following current EASL guidelines and baseline resistance testing leads to good SVR_{12} rates (85.9%).
- The majority of patients received a NS5A-containing 2nd line regimen, whose efficacy was affected by:
  1. Short duration of retreatment (above lack of ribavirin association)
  2. Presence of one or more NS5A RAS
  3. Previous NS5Ai-experience → Beware of reusing the same DAA class!!

Over time, they might increase in number …

- Optimization of retreatment regimens for DAA-failed patients takes advantage of baseline resistance testing.

  In this «fragile» population, regimens longer and with ribavirin (whenever possible) should be preferred (as recommended by current international guidelines).

WHO HCV Elimination Targets



- **Ambitious goals**
- **Requires National Action Plan → good data to design policy**

WHO. Draft WHO Global Hepatitis Strategy, 2016-2021.

Slide credit: clinicaloptions.com

Can We Avoid Genotyping?

- It's a delicate balancing

A Reasonable Compromise

Genotype only for:

Cirrhosis

Treatment-experienced (DAA/IFN)

Maximizing SVR in Individual Patient

- **Genotyping may be helpful**
- **Helpful in cirrhosis, particularly GT3**

Maximize SVR in the Population

- **Simplicity is key**
- **Genotyping adds some: cost, delay, and complexity**

Slide credit: clinicaloptions.com

Recommended Treatment Regimens

- **Genotype-specific**
  - Elbasvir/Grazoprevir: GT 1, 4
  - Ledipasvir/Sofosbuvir: GT 1, 4, 5, 6
- **Pangenotypic**
  - Sofosbuvir/Velpatasvir – GT 1-6
  - Glecaprevir/Pibrentasvir – GT 1-6
  - Sofosbuvir/Velpatasvir/Voxilaprevir – GT 1-6 (reserved for salvage therapy)

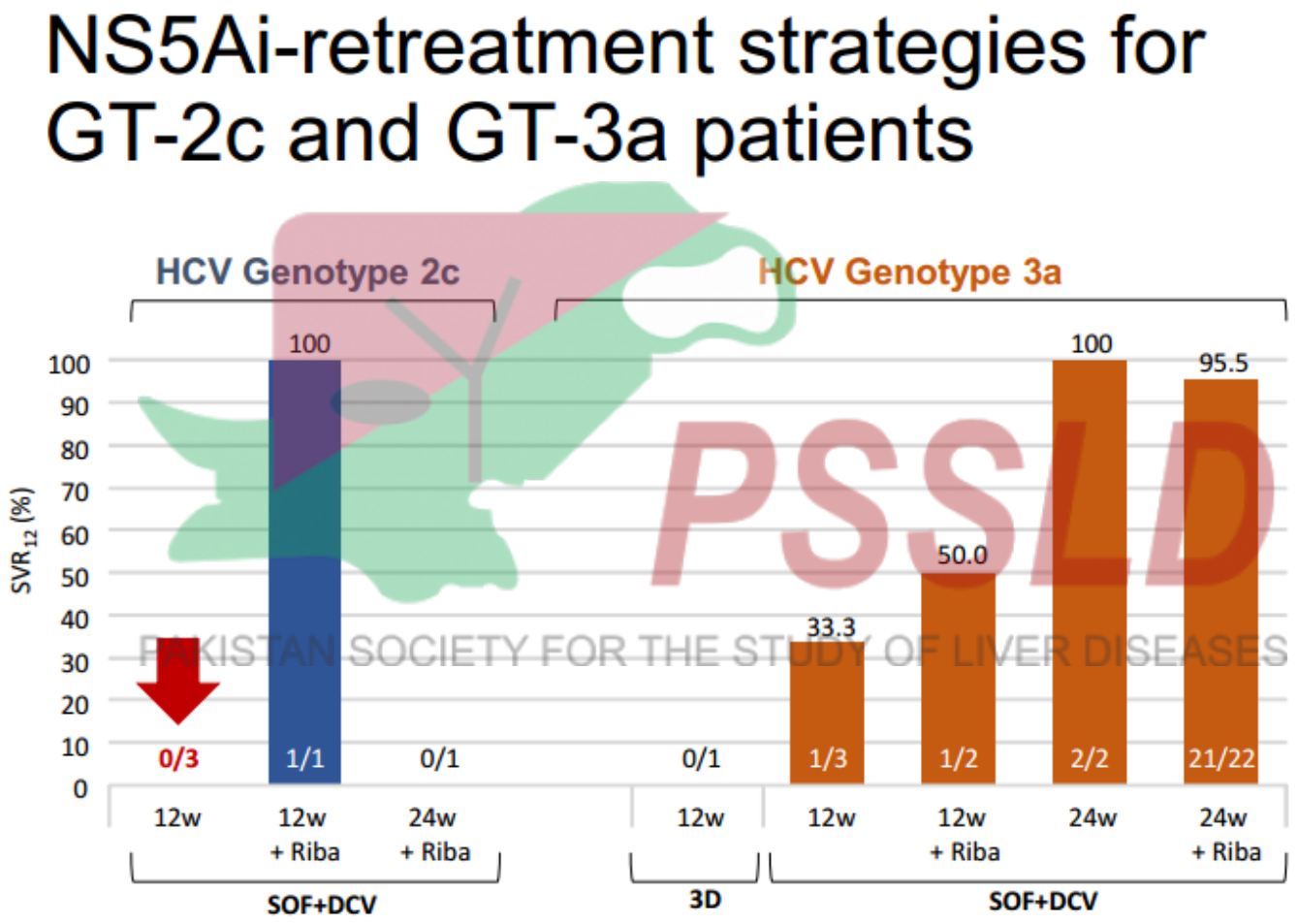
AASLD/IDSA. HCV Guidance. 2018.

Glecaprevir /Pibrentasvir

- Based on the Magellan-1 study, GLE/PIB has been approved in North America for salvage therapy of DAA-experienced GT1 patients

Poordad F, et al. Hepatology 2018;67:1253–1260

Vironet-C Italian Study



Cento V et al. Digestive Liver Dis 2017;49 (Issue 1 Suppl):e8

Table 2. Approved usage of SOF/VEL/VOX in DAA-naïve and DAA-experienced patients.

	Treatment duration	
	No cirrhosis	Compensated cirrhosis
Treatment-naïve patients[1]		
HCV genotypes 1–6	8 weeks	12 weeks[3]
PegIFN/RBV-experienced patients[1,2]		
HCV genotypes 1–6	8 weeks	12 weeks[3]
NS5A-experienced patients		
HCV genotypes 1–6	12 weeks	12 weeks

DAA, direct-acting antiviral; HCV, hepatitis C virus; NS5A-experienced, patients with prior HCV NS5A inhibitor failure; PEG-IFN, pegylated interferon; RBV, ribavirin.

[1] Approved in Europe only.

[2] Includes patient with prior PEG-interferon/ribavirin-experience.

[3] 8 weeks should only be considered in genotype 3 patients.

Journal of Hepatology 2018 vol. 69 j 1178–1187

Retreatment of DAA failures

- Retreatment strategy depends on initial regimen

Recommendations	Grade of evidence	Grade of recommendation
After failure of PEG-IFNα + RBV, SOF + PEG-IFNα/RBV or SOF + RBV • Retreat according to recommendations for TE patients, by HCV genotype	A	1
HCV resistance testing after failure of any DAA-based regimen (excluding regimens with SOF as the only DAA) is a useful guide to retreatment	B	2
After failure of DAA (PI and/or NS5A inhibitor)-containing regimen		
• First-line retreatment – SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis) – SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis)	A B	1 2
• Patients with predictors of poor response, SOF + GLE/PIB for 12 weeks: – Advanced liver disease – Multiple courses of DAA-based treatment – Complex NS5A RAS profile	B	2
• **Very difficult-to-cure patients:† SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV for 12 weeks or for 16 or 24 weeks**	C	2

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance;
†Patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a PI and/or an NS5A inhibitor
EASL CPG HCV. J Hepatol 2018;69:461–511.