Therapy of chronic hepatitis C: personalizing decisions.

Update and clinical cases

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Disclosures

- **Consultant: ViiV, Bristol-Myers Squibb, Abbvie, Gilead, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim.**
- **Speaker at company-sponsored events: ViiV, Roche, Bristol-Myers Squibb, Gilead, Abbvie, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim.**
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- **Grants for research: ViiV, Roche, Gilead, Abbvie, Bristol-Myers Squibb, Janssen, Merck Sharp & Dohme and Boehringer Ingelheim.**

Therapy of HCV session

- **Objective: To discuss several points on the current treatment of hepatitis C.**
- **Procedures:**
  - **2 clinical cases**
  - **Questions with several possible answers**
- **Votes and opinions:**

Clinical case 1

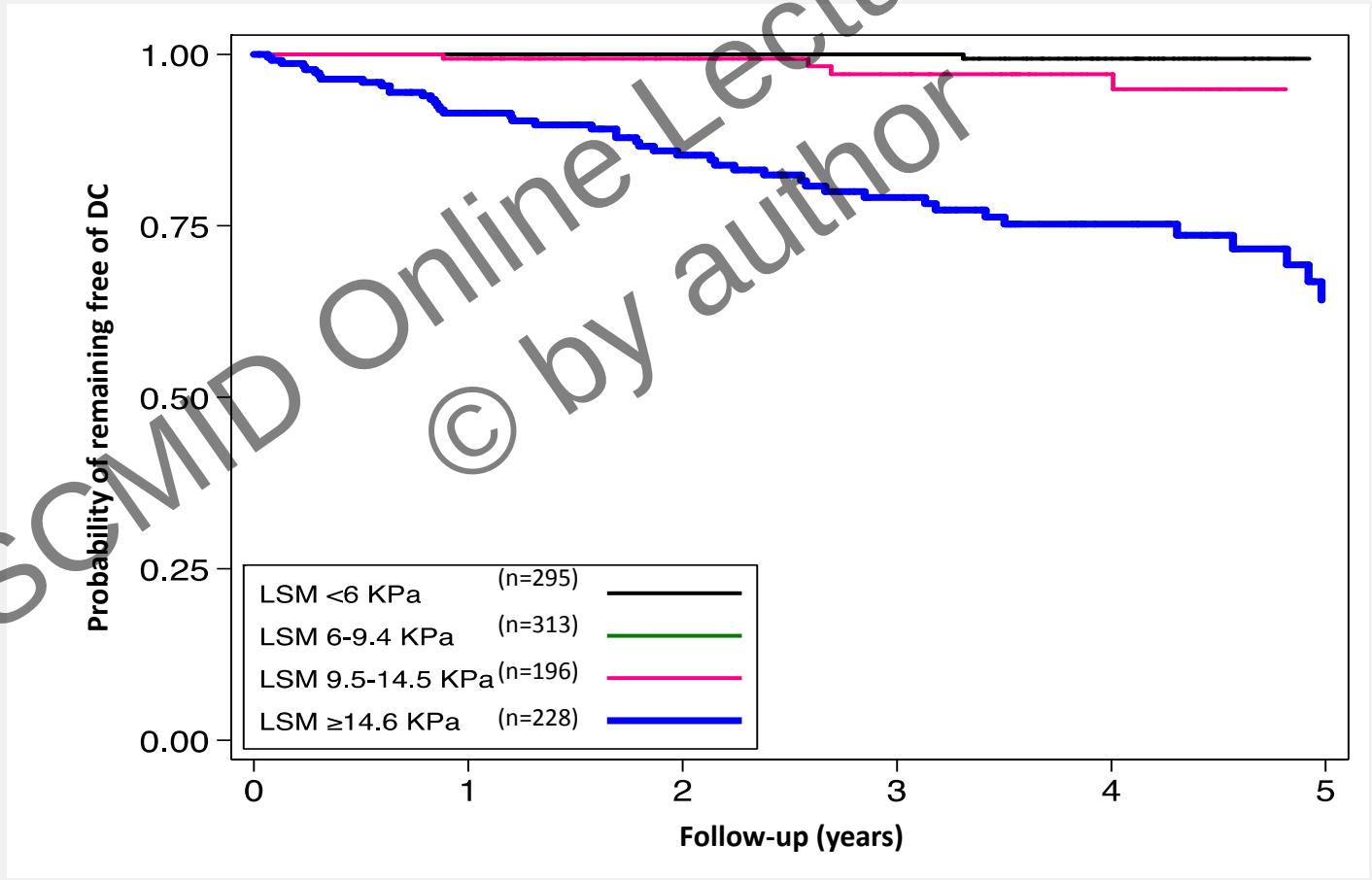
- 50 y.o. male patient
- PWID for 6 months, 28 year ago. No present toxic use.
- In a routine blood test: ALT 59 mU/mL, AST 68 mU/mL, GGT 62 mU/mL, total bilirubin 0.9 mg/ml.
- GP started a liver disease work-up
  - HBsAg negative; HBsAb positive; HBcAb positive.
  - HCVAb: Positive.
- Referred to our Unit

Clinical case 1. Question 1.

- **HCV RNA: 6.800.000 IU/mL**
- **HCV genotype (LiPA 2): 1b**
- **The patient is willing to start treatment against HCV infection**
- **Should he be treated?**

Reasons to treat HCV infection

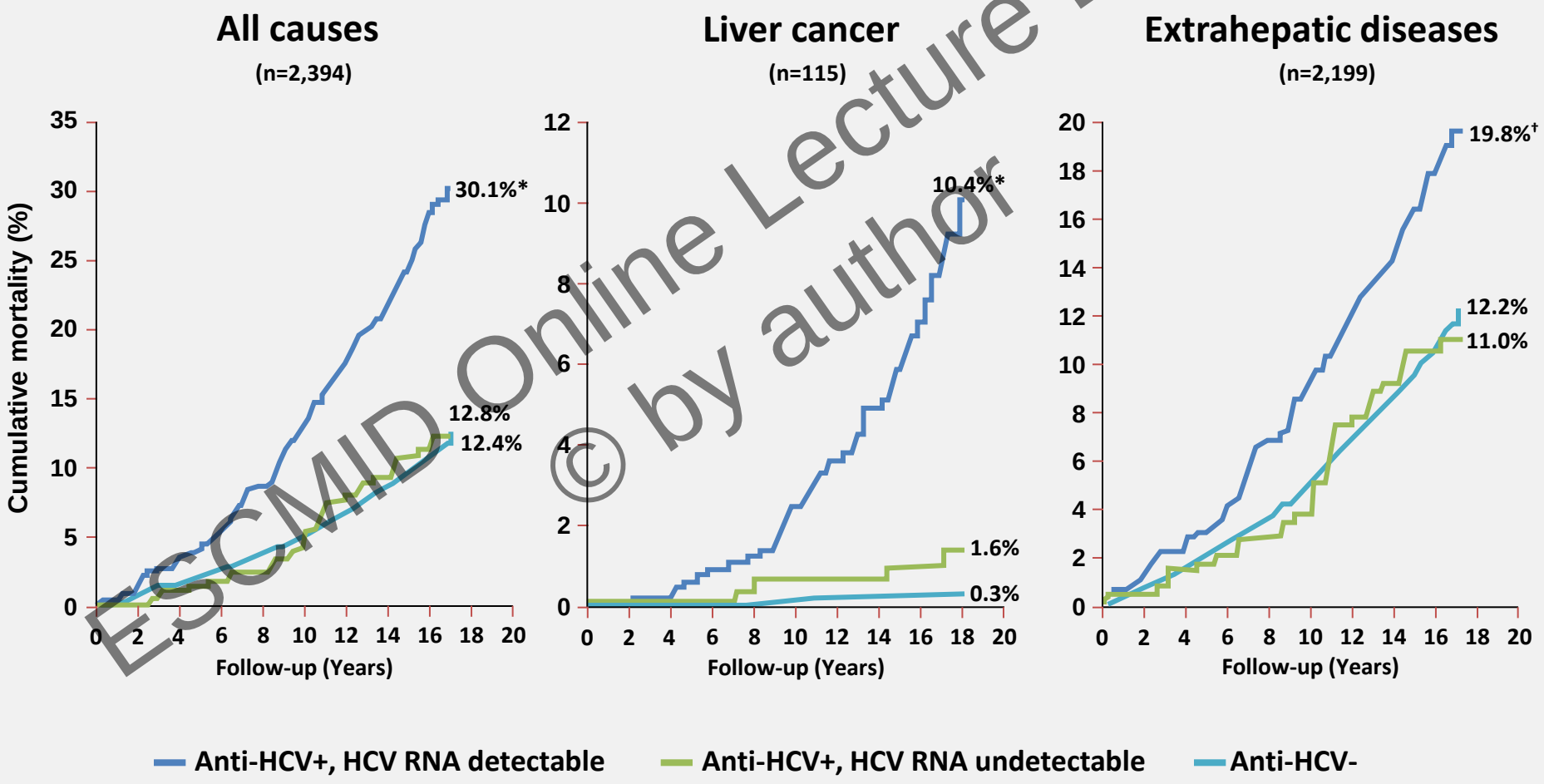
Probability of developing a first liver decompensation, according to baseline fibrosis (as measured by liver stiffness) in HIV/HCV-coinfected patients. HEPAVIR Cohort.



Macías J, et al. Hepatology 2014.

Reasons to treat HCV infection

HCV infection increases liver-related and extrahepatic mortality



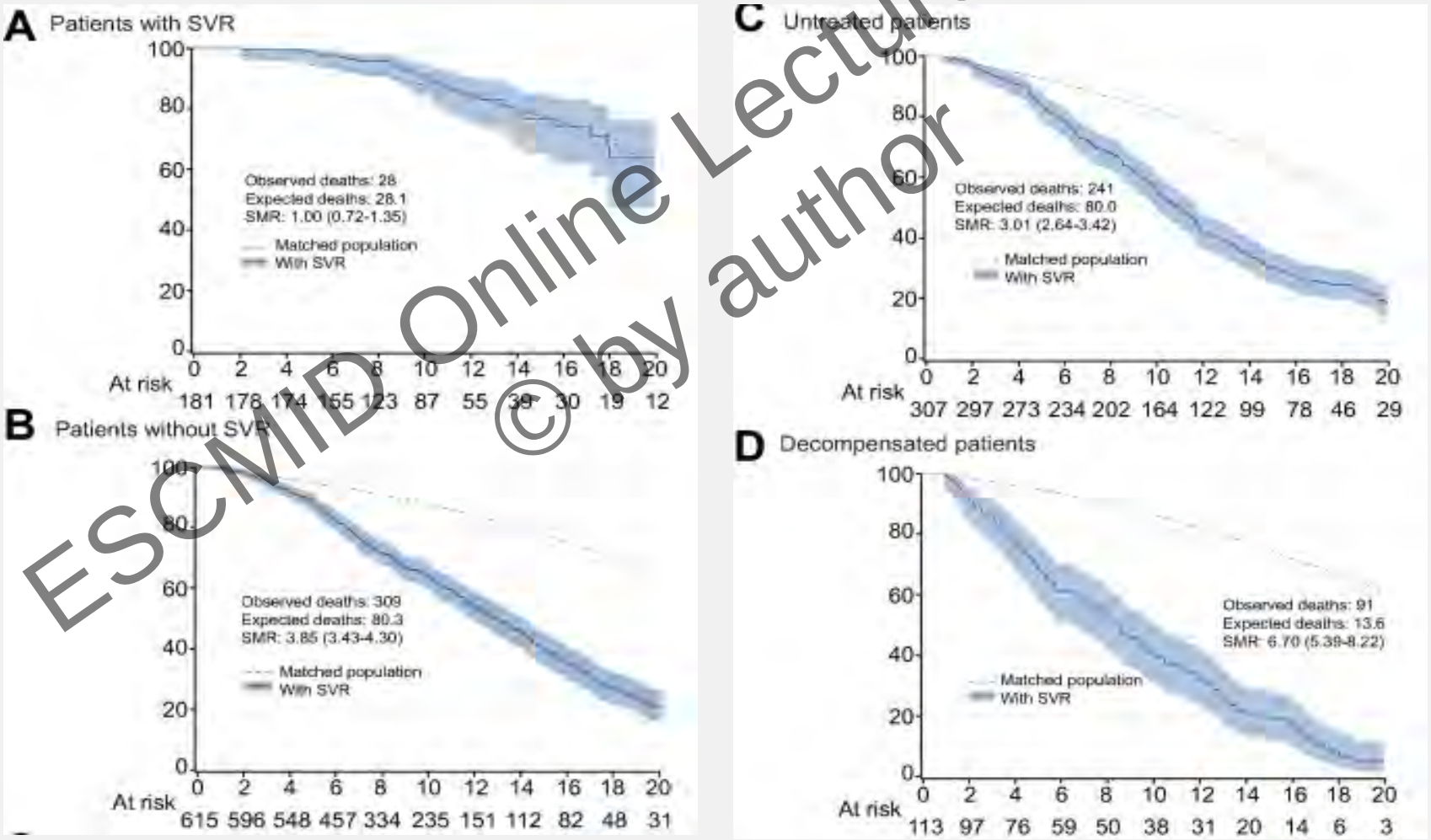
*P<0.001 for comparison among all 3 groups and P<0.001 for HCV RNA detectable vs. undetectable.
†P<0.001 for comparison among all 3 groups and P=0.002 for HCV RNA detectable vs. undetectable.

Lee MH, et al. J Infect Dis 2012;206:469–77.

Reasons to treat HCV infection

Achieving SVR matches mortality of HCV-infected cirrhotic patients with that of the general population

Mortality of Italian patients with cirrhosis in several conditions in comparison with an age and sex matched general population

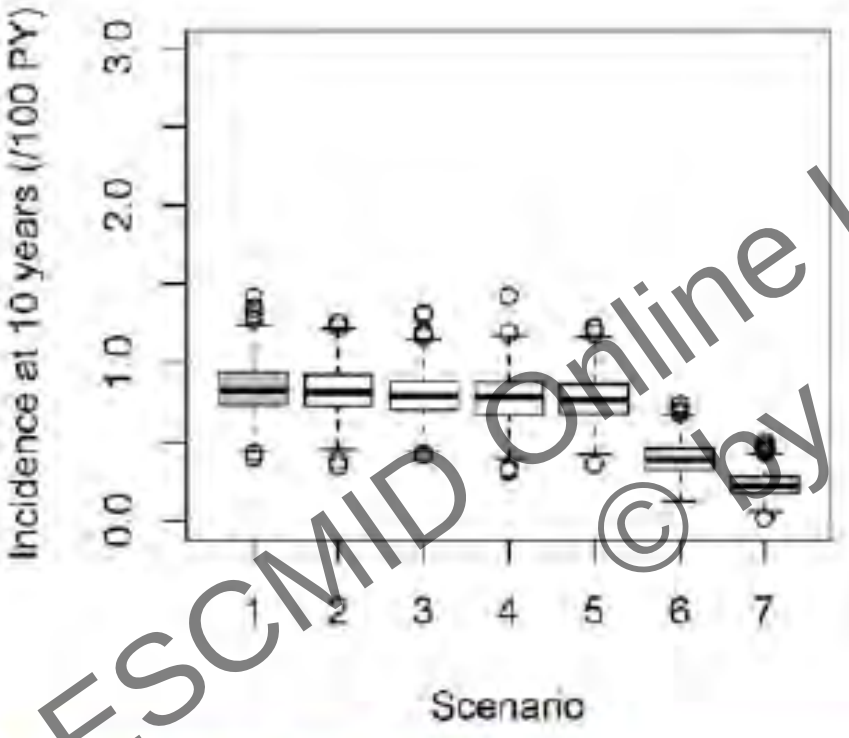


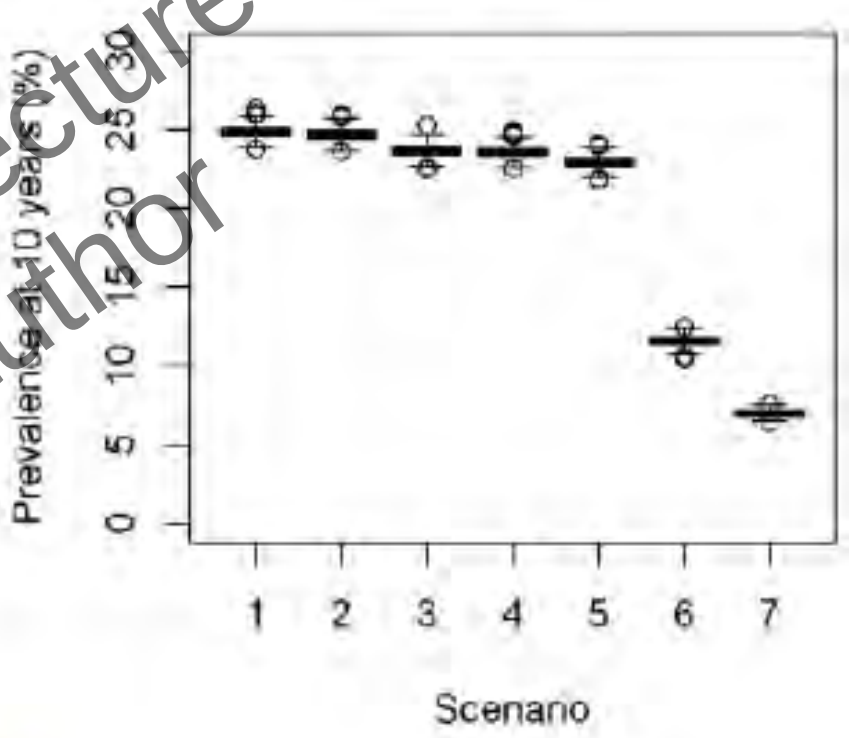
Bruno S, et al. J Hepatol 2016 ; 64: 1217

Reasons to treat HCV infection

Universal treatment may lead to HCV worldwide eradication

Impact of Different Interventions on HCV Prevalence/Incidence in PWID





1.-Current cascade of care (reference)
2.-Improvement of HCV testing
3.-Improvement of linkage to care (LTC)
4.-Improvement of testing and LTC
5.-Improvement of adherence to treatment
6.-Treatment initiated from F0
7.-Improvement of the entire cascade of care (combination 4, 5, 6)

Cousien A, et al. Hepatology 2016

Clinical case 1. Question 1.

- **HCV RNA: 6.800.000 IU/mL**
- **HCV genotype (LiPA 2): 1b**
- **The patient is willing to start treatment against HCV infection**
- **Should he be treated?**

All HCV-infected patients should be considered candidates to therapy with DAA. However, usually, patients are prioritized, in order to optimize health resources.

Factors determining the priority for treatment

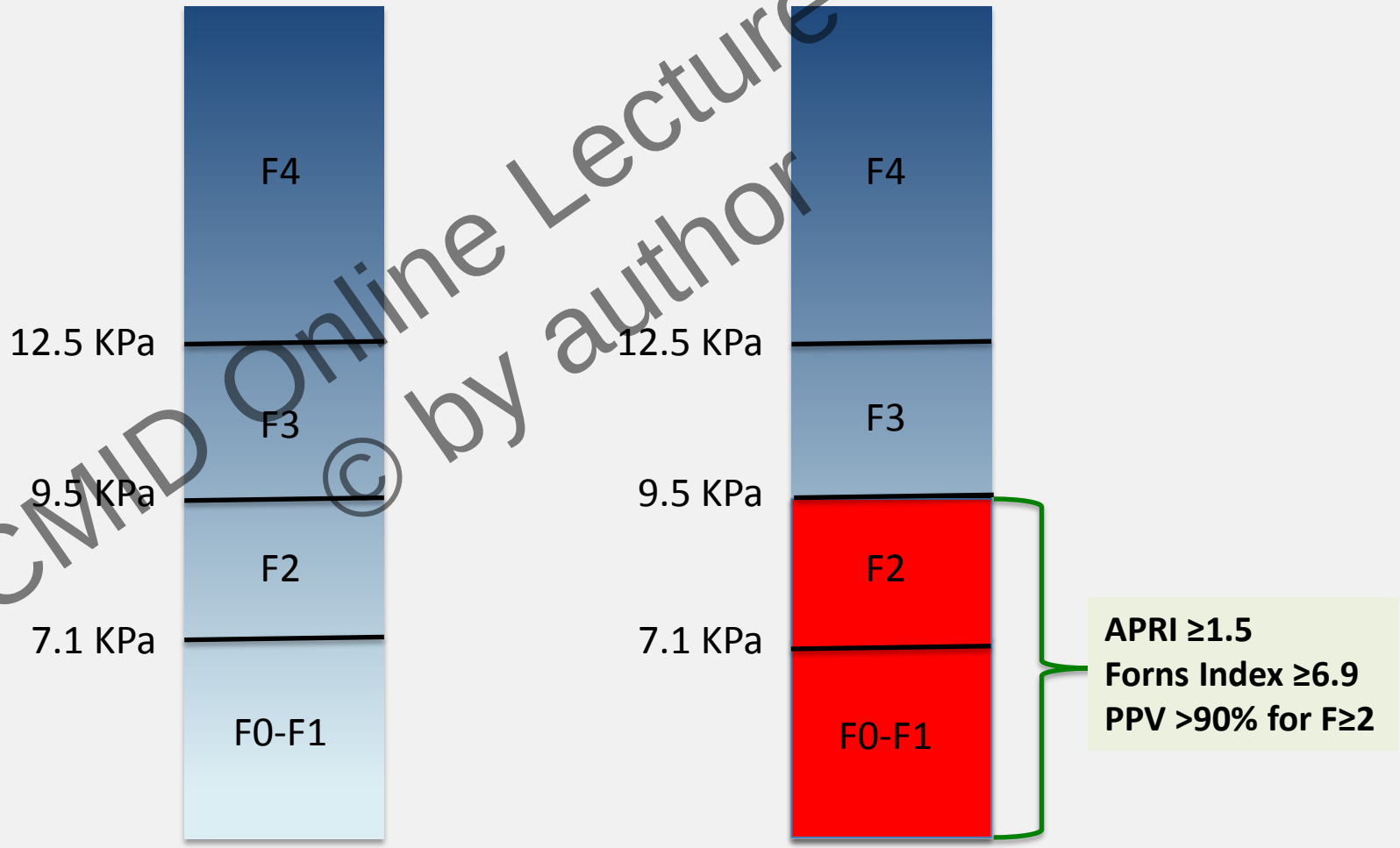
- Liver fibrosis ≥F2
- Extrahepatic manifestations
- Women willing pregnancy
- High risk of transmission
- Other conditions: HIV or HBV coinfections, diabetes, transplants, porphyria cutanea tarda.
- Local regulations on HCV therapy

Clinical case 1. Question 2.

What of the following procedures would you use to assess liver fibrosis in a HCV-infected patient?

1. **Liver biopsy**
2. **Blood fibrosis markers: APRI, Forns index, FIB-4**
3. **Liver elastography (FibroScan, ARFI)**
4. **CT scan**
5. **2 and 3**

Simple blood fibrosis markers enhance the diagnostic performance of FibroScan in low fibrosis stages



Castera L, et al. Gastroenterology 2005; 128: 343-350.
Macias, J. J Hepatol 2008; 49: 916–922

Clinical case 1. Question 2.

What of the following procedures would you use to assess liver damage in a HCV-infected patient?

1. **Liver biopsy**
2. **Blood fibrosis markers: APRI, Forns index, FIB-4.**
3. **Liver elastography (FibroScan, ARFI)**
4. **CT Scan**
5. **2 and 3**

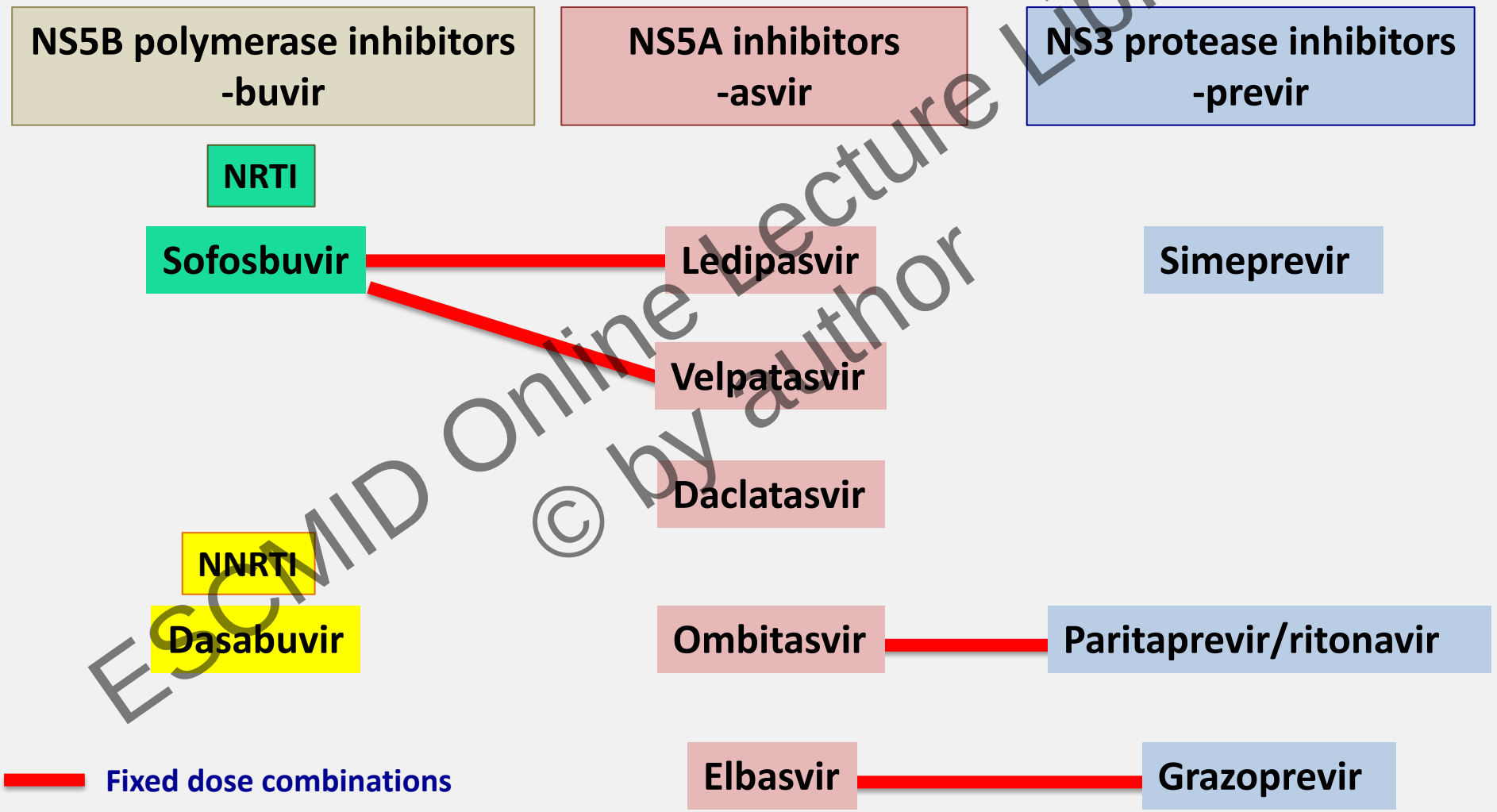
Clinical case 1

- **FibroScan: LS: 17.2 kPa**
- **APRI: 1.98**
- **Forns index: 8.1**

Clinical case 1. Question 3.

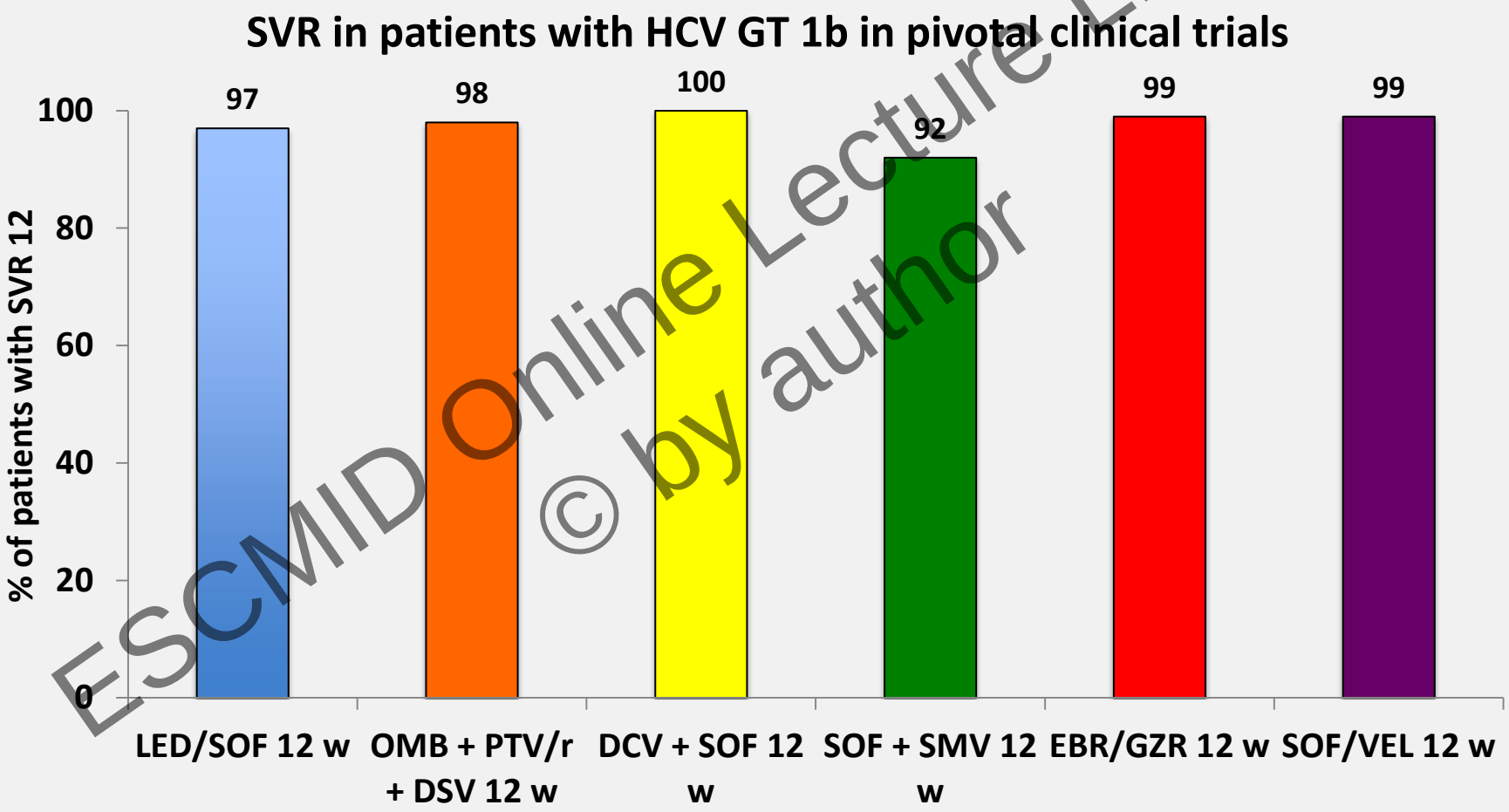
- **What DAA combination would you start in this patient?**
  1. **LED/SOF 12 w**
  2. **OMB + PTV/r + DSV 12 w**
  3. **DCV + SOF + RBV 12 w**
  4. **SOF + SMV + RBV 12 w**
  5. **EBR/GZR 12 w**
  6. **SOF/VEL 12 w**

Drugs and families currently used in HCV therapy



- Ribavirin has to be included in some regimens in subjects with lower rates of SVR.
- Peg-IFN is currently recommended only in very specific cases, such as in patients with GT3 and failure to DAA.

Efficacy of different combinations for HCV genotype 1b infection in naïve patients



Afdhal N, et al. N Engl J Med 2014; Lawitz E, et al. Gastroenterology 2015; Wyles DL, et al. N Engl J Med 2015; Kwo P, et al. Hepatology 2016; Zeuzem S, et al. Ann Intern Med 2015; Feld JJ, et al. N Engl J Med 2015.

Tolerability of DAA combinations depends on the need of RBV

Tolerabity of EBR/GZR in the EDGE-TE Study

	12 WEEKS		16 WEEKS	
	No RBV, n = 105	RBV, n = 104	No RBV, n = 105	RBV, n = 106
Serious adverse event, n (%)	4 (3.8)[1]	3 (2.9)[2]	3 (2.9)[3]	4 (3.8)[4]
Death, n (%)	0	0	0	0
Discontinued study medication due to adverse event, n (%)	1 (1.0)[5]	1 (1.0)[6]	0	5 (4.6)[7]
Hemoglobin <10 g/dL, n (%)	0	9 (8.7)	0	22 (20.8)
Total bilirubin >5xbaseline, n (%)	0	0	0	0
Late ALT/AST >5xULN*, n (%)	0	1	4	0
Most common AEs**, n (%)				
Fatigue	20 (19.0)	28 (26.9)	17 (16.2)	32 (30.2)
Headache	22 (21.0)	21 (20.2)	20 (19.0)	20 (18.9)
Nausea	9 (8.6)	15 (14.4)	4 (3.8)	18 (17.0)

* ALT/AST >5X upper limit of normal after TW4 after normalization; **Most common = Overall frequency >10%

SAEs: [1]Unstable angina/coronary artery disease; hip fracture; sudden hearing loss; ascites; [2]abdominal pain/transient ischemic attack; infectious colitis; uterine polyp; [3]overdose; lymphocytosis; loss of consciousness; [4]tibia fracture; rib fracture; anemia; colitis/gastrointestinal inflammation.

Discontinued study medications due to adverse event: [5]ascites, [6]emotional lability day 35; [7]portal vein thrombosis; palpitations; colonic angioedema; drug abuse; suicidal ideation

Kwo P, et al. ILC 2015, Viena

Factors to be considered for making the treatment regimen choice

- Virus
  - HCV genotype (if 1, also subtype).
  - HCV RNA load.
  - Presence of RAVs.
- Host
  - Cirrhosis.
  - History of HCV treatment and response.
  - History of decompensations
- DAA combination
  - Need of RBV
  - Duration of treatment
- Other factors
  - Health system regulations on HCV therapy
  - Price of drugs

Recommended regimens for treatment of patients with genotype 1: 2016 AEEH/SEIMC guidelines

Preferred combinations **Alternative combinations**

Drug combination	GT 1 b No cirrhosis	GT 1 b Cirrhosis	GT 1a No cirrhosis	GT 1a Cirrhosis
DCV+SOF	12w (A1)	12w + RBV (B1)	12w (A2)	12w + RBV (A2)
EBR/GZR*	12w (A1)	12w (No Child B-C) (A1)	12w (naïve, relapser) (A1); 16w+RBV* (non responders) (A1)	12w+RBV (RAVs?) (A1); 16w+RBV (RAVs) (A1)
LDV/SOF	12w (A1) (8w naïve, VL<6 MUI)(A2)	12w naïve (A1); 12w+RBV or 24w NR (A1)	12w (A1) (8w naïve, VL<6 MIU)(A2)	12w naïve (A1); 12w+RBV 24w NR (A1)
OBV/PTV/r+DSV	12w (A1)	12w (No Child B-C) (A1)	12w+RBV (A1)	12w+RBV* naïve, relaapsers (A1); 24w+RBV Non responders (A1)
SMV+SOF	12w (A1)	12w + RBV (B2)	12w (A1)	12w + RBV (no Q80K) (A1)
SOF/VEL*	12w (A1)	12w (A1)	12w (A1)	12w (A1)

*Still unavailable

Non-responders to TVR o BOC:
EBR/GZR + RBV 12w (A1), 16w (if RAVs to NS5A) (B3)
LDV/SOF + RBV 12w (A1), 24w (if intolerance to RBV) (A1)

http://www.seimc.org/contenidos/gruposdeestudio/gehep/dcientificos/documentos/gehep-dc-2016-Manejo_HepatitisC.pdf

Clinical case 1. Question 3.

- **What DAA combination would you start in this patient?**
  1. **LED/SOF 12 w**
  2. **OMB + PTV/r + DSV 12 w**
  3. **DCV + SOF + RBV 12 w**
  4. **SOF + SMV + RBV 12 w**
  5. **EBR/GZR 12 w**
  6. **SOF/VEL 12 w**

Clinical case 1

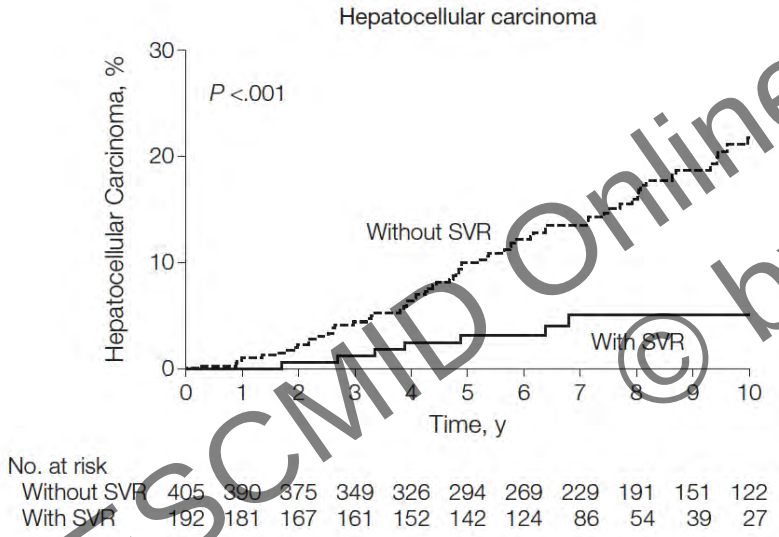
- **The patient received OBV/PTV/r+DSV 12 w**
- **12 w after completing therapy, plasma HCV-RNA was undetectable**
- **LS was 11.5 kPa**

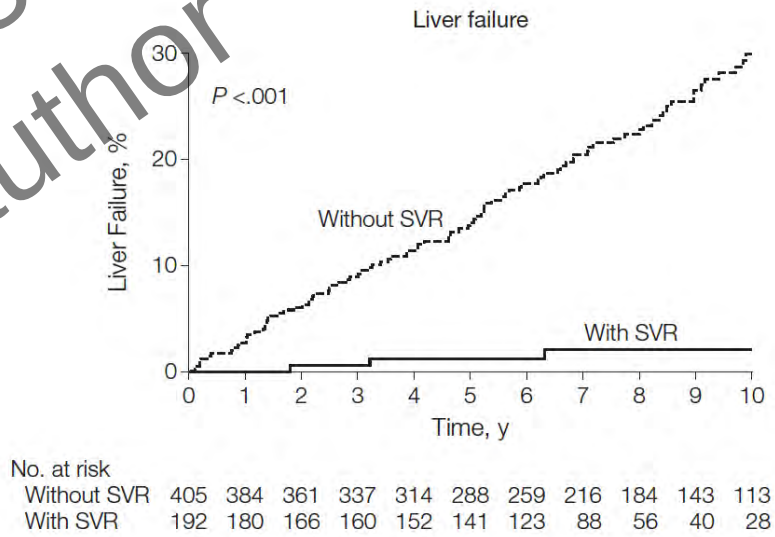
Clinical case 1. Question 4.

- **Once SVR is confirmed, may we discontinue the follow-up in this patient?**
    1. **Yes, HCV infection is cured and reinfection is unlikely.**
    2. **No, surveillance for liver complications will still be required.**

Surveillance for liver complications should be maintained in patients with cirrhosis and SVR in the long-term

Risk of HCC and liver failure in subjects with advanced fibrosis achieving SVR with PR





Screening for liver cancer and esophageal varices should continue in patients with cirrhosis despite attaining SVR.

Van de Meer AJ, et al. JAMA. 2012; 308: 2584-2593

Clinical case 1. Question 4.

- **Once SVR is confirmed, may we discontinue the follow-up of this patient?**
    1. **Yes, HCV infection is cured and reinfection is unlikely.**
    2. **No, surveillance for liver complications will still be required.**

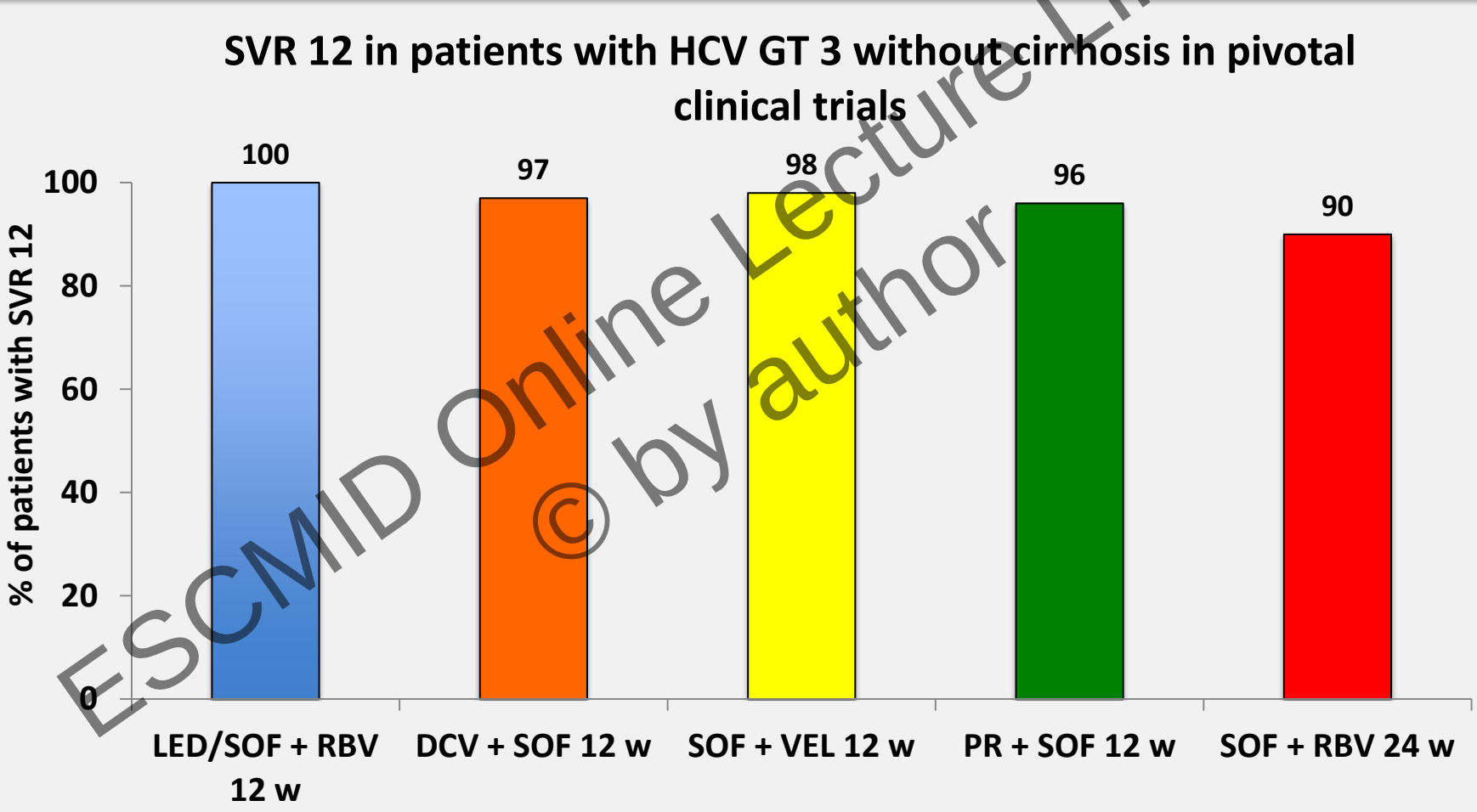
Clinical case 2

- 46 y.o. male patient
- Former PWID.
- HIV infection, CDC stage A2, on TDF+FTC+EVG-COBI. No other current medication.
- CD4 cell counts 868; HIV-RNA load <20 c/mL.
- Infected with HCV genotype 3a, treatment naïve.
- Plasma HCV-RNA 6.890.000 IU/mL.
- LS: 10.6 kPa.

Clinical case 2. Question 1.

- **What DAA combination would you start in this patient?**
  1. **LED/SOF + RBV 12 w**
  2. **DCV + SOF 12 w**
  3. **SOF/VEL 12 w**
  4. **Peg-IFN + RBV + SOF 12 w**
  5. **SOF + RBV 24 w**

Efficacy of different combinations for HCV genotype 3 infection in naïve patients



Gane EJ, et al. Gastroenterology 2015; Nelson DR, et al. Hepatology 2015; Foster GR, et al. N Engl J Med 2015; Foster GR, et al. Gastroenterology 2015.

Recommended regimens for treatment of patients with genotype 3: 2016 AEEH/SEIMC guidelines

Preferred combinations Alternative combinations

Drug combination	No cirrhosis	Cirrhosis
DCV+SOF	12w (A1)	12w + RBV (B1) or 24w ± RBV (B1)
SOF/VEL*	12w (A1)	12w (A1)

*Still unavailable

Non-responders to PR or SOF + RBV
SOF/VEL 12s (A1)

Non-responders to DCV + SOF or SOF/VEL
PR + SOF 12 w (B3)

http://www.seimc.org/contenidos/gruposdeestudio/gehep/dcientificos/documentos/gehep-dc-2016-Manejo_HepatitisC.pdf

Clinical case 2. Question 1.

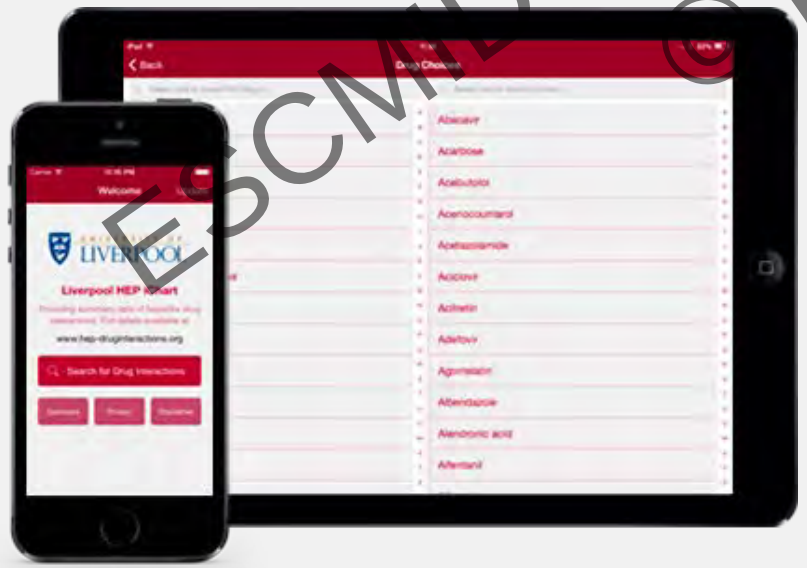
- **What DAA combination would you start in this patient?**
  1. **LED/SOF + RBV 12 w**
  2. **DCV + SOF 12 w**
  3. **SOF/VEL 12 w**
  4. **Peg-IFN + RBV + SOF 12 w**
  5. **SOF + RBV 24 w**

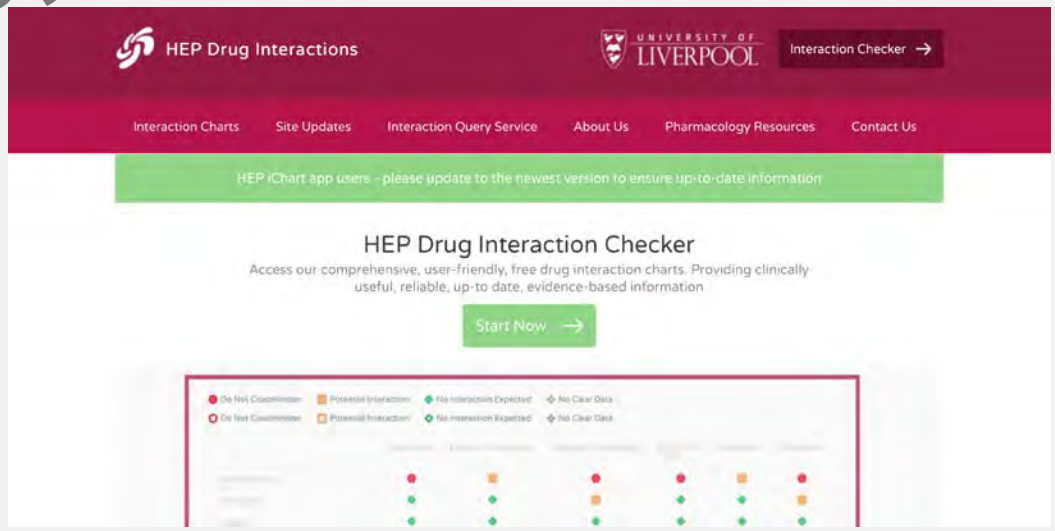
Clinical case 2. Question 2.

- **May this patient receive TDF + FTC + EVG/COBI and DCV + SOF simultaneously?**
  1. **Yes, without any particular consideration**
  2. **Yes, but renal function must be carefully monitored**
  3. **Yes, but DCV dosage should be reduced**
  4. **No, ART should be modified before starting SOF + DCV**
  5. **No, an alternative HCV therapy is recommended**

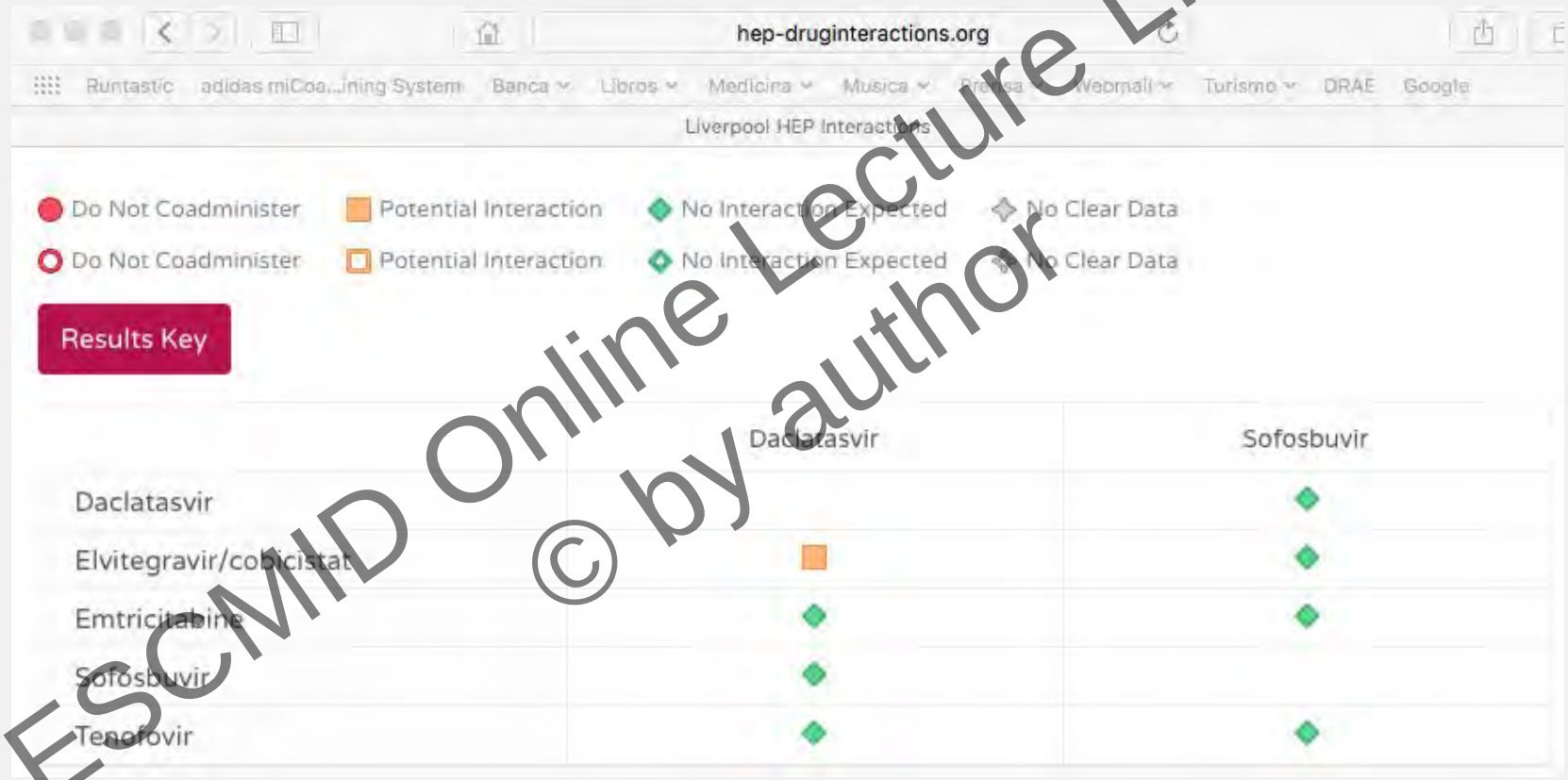
DDI management in patients taking DAA

- **DDIs between DAAs and other drugs are very common, particularly when PI-including regimens are used.**
- **Before starting a treatment with DAA, particularly in HIV-infected patients taking ART, the likelihood of DDI should be carefully checked using a computer tool.**





Clinical case 2



Summary:
Coadministration has not been studied but is expected to increase daclatasvir concentrations due to inhibition of CYP3A4 by cobicistat. The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with cobicistat.

Clinical case 2. Question 2.

- **May this patient receive TDF + FTC + EVG/COBI and DCV + SOF simultaneously?**
  1. **Yes, without any particular consideration**
  2. **Yes, but renal function must be carefully monitored**
  3. **Yes, but DCV dosage should be reduced**
  4. **No, ART should be modified before starting SOF + DCV**
  5. **No, an alternative HCV therapy is recommended**

HCV therapy in the DAA era
Take home messages

- All HCV-infected patients have to be treated, but prioritization is required in order to maximize efficiency.
- Treatment should be individualized on the basis of viral, host, drug-related, economic and regulatory data.
- IFN-free DAA combinations (sometimes with RBV) are currently the base of HCV treatment.
- Most patient will achieve SVR
  - Patients without advanced liver fibrosis and no ongoing risk factor do not require long-term follow-up afterwards.
  - In subjects with cirrhosis, continuous surveillance for liver complications is needed.
- In patients with co-medication (HIV-coinfected), a careful checking for potential DDI have to be conducted before starting therapy.