Interactive Case Discussion
Difficult to treat hepatitis C patient (multiple treatments and cirrhosis)

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First, An Easy-to-Treat Patient

- 44-year-old, woman
- Anti-HCV (+) during screening (before operation)
- HCV-RNA 140 000 IU/mL
- Genotype 1b
- US: normal

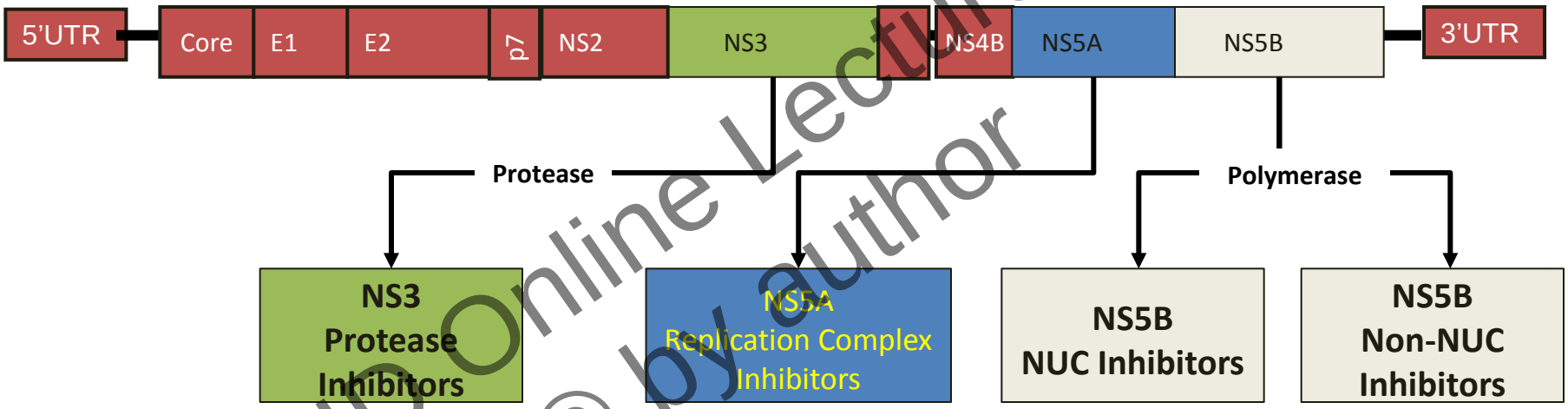
- Do you get a liver bx?
- Do you treat?
  - If yes, with what?

- Every individual with an HCV-RNA positivity should be considered for treatment.
  - Liver biopsy or non-invasive test may provide information about the severity of the disease
  - Absence of cirrhosis affects the SVR rates, and thus treatment plan (adding ribavirin, prolonging duration) may change

With what?
The guidelines…

- Naïve, genotype 1b
  - AASLD
    - SOF+LED, SOF+SIM, Abbvie Combo (3D)
  - EASL
    - Peg-IFN+R+SOF, Peg-IFN+R+SIM
    - SOF+LED, SOF+SIM, SOF+DAC, Abbvie Combo

Directly Acting Antivirals (DAAs) in HCV



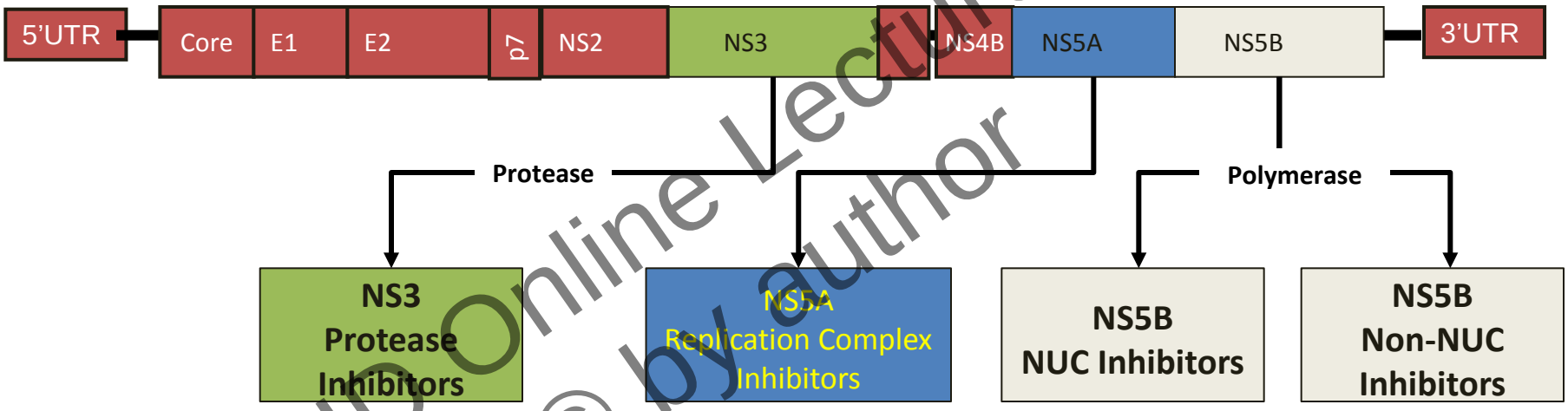
Telaprevir
Boceprevir
Simeprevir
Asunaprevir
Paritaprevir+r
Grazoprevir

Daclatasvir
Ledipasvir
Ombitasvir
Elbasvir

Sofosbuvir

Dasabuvir

Directly Acting Antivirals (DAAs) in HCV



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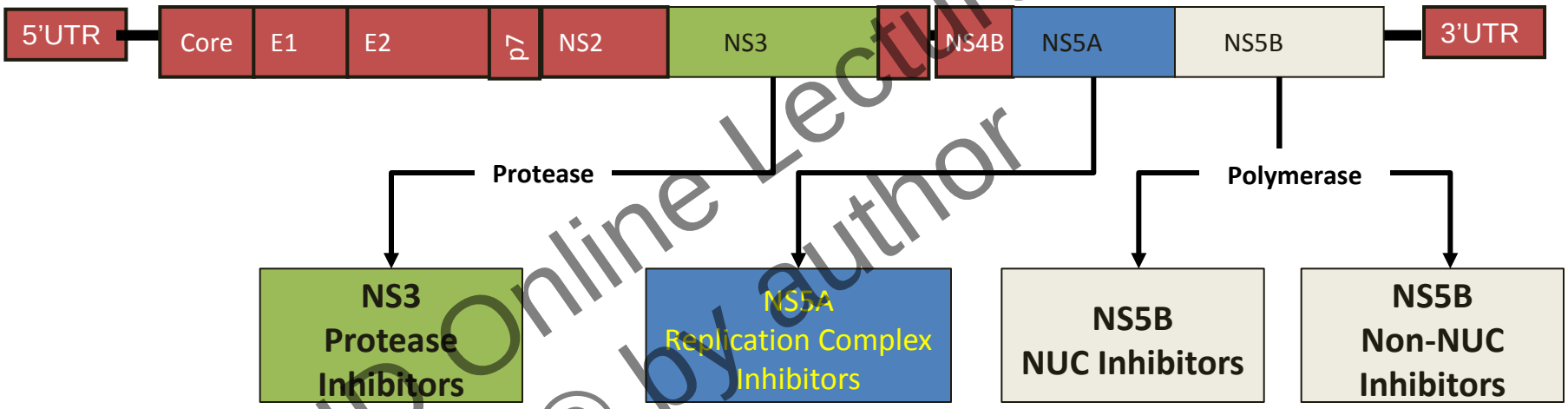

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Daclatasvir ---- **Sofosbuvir**
Ledipasvir
Ombitasvir
Elbasvir

Dasabuvir

- Prescribed paritaprevir+ritonavir+ombitasvir and dasabuvir
- Viekirax®1x2 and Exviera® 2x1

- Month 1: HCV-RNA: undetectable
- Month 3: HCV-RNA: undetectable
- Follow-up month 3: HCV-RNA: undetectable

=Sustained virological response

Conclusion

- HCV treatment in naïve, non-cirrhotic patients is easy
  - ≅100% SVR, ≤12 weeks
- Cost, availability?

Peg-IFN + Riba: Still an option?

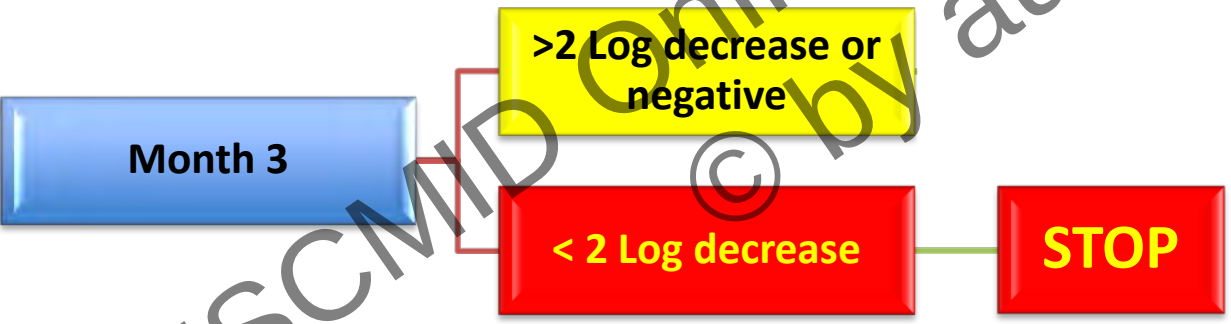
- Admitted in 2011
- 68-year-old, male
- A screening before gallbladder operation
  - anti-HCV (+)
- HCV-RNA: 1 040 000 IU/mL
- Genotip 1

- ALT 71 U/L
- AST 79 U/L
- Alb 2.9 mg/ml
- Platelets 99 000/mm^3
- US:
  - Liver: irregular borders; coarse, granular, heterogeneous parenchyma
  - Spleen 129 mm
  - No ascites

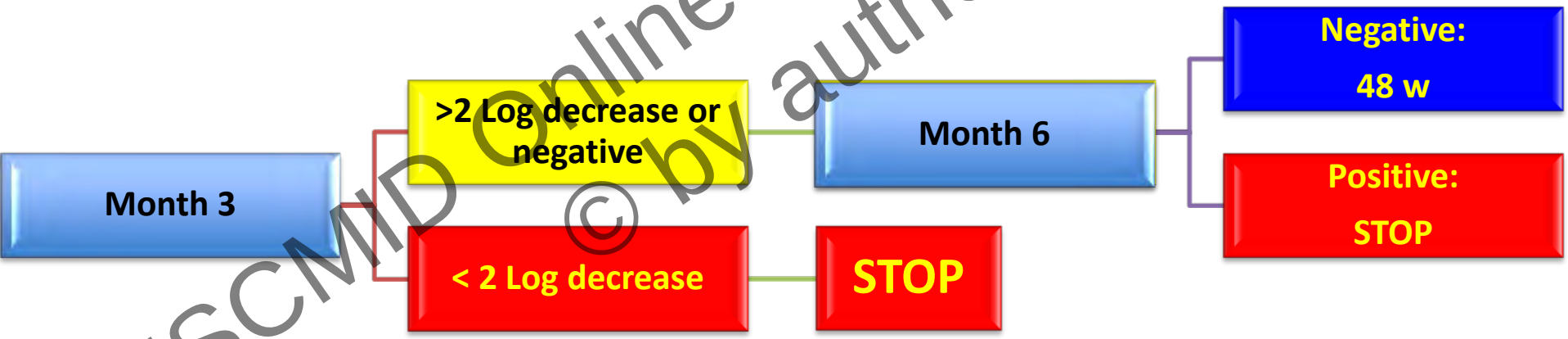
- Do you treat this patient with PEG-IFN+Riba?
  - 68 y-o, US findings of cirrhosis, low platelets, low albumin level

- PEG-IFN alfa2b 100 mcg/week + ribavirin 1000 mg/day
- Baseline HCV-RNA: 1,040,000 IU/mL

Genotype 1, Peg-IFN and Ribavirin



Genotype 1, Peg-IFN and Ribavirin



- PEG-IFN alfa2b 100 mcg/week + ribavirin 1000 mg/day
- Baseline HCV-RNA: 1,040,000 IU/mL
- Week 12 HCV-RNA: 19,100 IU/mL
- Treatment was not discontinued; 15 days later HCV-RNA: 2830 IU/mL

- Platelet count: 60 000-90 000 /mm^3
- Hb values: 10-12 gr/ml

- Month 5
- Admitted to ER with fever, fatigue, fever, and right upper abdominal pain
  - Confused
  - Peripheral edema
  - Ascites

- US: perihepatic abscess, ascites
- Lab
  - ALT 48 U/L
  - AST 89 U/L
  - Alb: 2.7 gr/ml
  - CRP 10x

- Do you insist on Peg-IFN+Riba?

Peg-IFN+ribavirin discontinued

- Ertapenem
- Spironolactone
- Furosemide
- Lactulose

initiated

- Discharged and referred to an liver transplantation center.
- Live-related liver was transplanted.

Conclusion

- A compensated cirrhotic patient may not wait for new treatment options
  - May decompensate during waiting!
- A compensated cirrhotic patient may decompensate with interferon-containing treatment.

Transplantation… solves every problem?

- 55-year-old, woman
- Admitted with anti-HCV (+) during screening in 2010
  - HCV-RNA: 3,760,000 IU/mL
  - Genotype 1b
  - Platelets 100,000/mm^3
  - US: Liver: irregular borders, coarse parenchyma, Spleen: 13 cm.

- Peg-interferon and ribavirin in Dec 2010
  - Baseline HCV-RNA:3 760 000 IU/mL,
  - March 2011: 1 390 000 IU/mL
- Treatment discontinued…

Null responder

- Follow-up without treatment
- Screened for an all-oral HCV regimen (Phase 3 trial)
    - Excluded because of significantly high alpha-fetoprotein level
    - Re-screened: AFP is high
        - US/MRI: No findings of hepatocellular carcinoma

- In 2012, admitted to ER with ascites and hepatic encephalopathy
  - Decompensation

- 13 June 2013: Live-related (her son) liver transplantation

- Post-transplant period
  - Liver enzymes are high (ALT 200-350 U/L, AST 300-700 U/L)
  - HCV-RNA 24 400 000 IU/mL (9 Jan 2014)

- 9 April 2014
- Liver bx (Ishak)
  - HAI: 15
  - F:5

Relapse and cirrhosis in transplanted liver

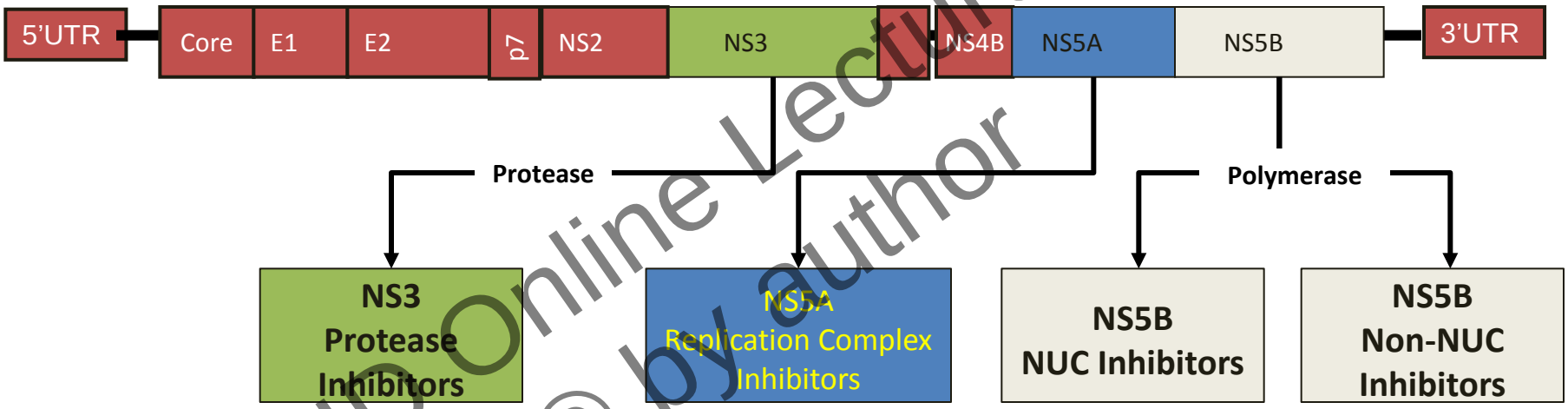
30 Apr 2014
Application for Compassionate Use Program

	Weight (Kg)	65
Primary diagnosis	HCV-decompansated cirrhosis-liver transplantation-relapse of HCV infection in transplanted liver	
HCV infection information	**Genotype/subgenotype**	1
	HCV RNA	24 400 000 IU/mL (9 Jan 2014)
Disease scores	**Child-Pugh Category**	A
	MELD score	7
Laboratory tests (please include units)	**ALT**	335 U/L
	AST	700 U/L
	Hemoglobin	107 g/L
	Platelets	84 x10^9/L
	INR	1.1
	Total bilirubin	28.215 µmol/L
	ANC	2.82 x10^3/µL
	Albumin	3.5 g/L
	Creatinine Clearance	196 mL/min
	Alkaline Phoshatase	256 U/L
HIV / HBV status (negative/positive)	**HIV serology**	Negative
	HBV serology	Anti-HBs: 100 mIU/mL
Date(s) of most recent **liver biopsy/staging of liver disease** by alternative noninvasive	8 Apr 2014: (transplanted liver): Inflammation score: 15/18, Fibrosis score: 5/6 (Ishak's score), incomplete cirrhosis. Re-transplantation is under consideration.	

- Daclatasvir and asunaprevir were initiated in 10 Sep 2014

- Daclatasvir+ Asuneprevir: Daklinza 60 mg (1x)+Sunvepra 100 mg (2x1)

Directly Acting Antivirals (DAAs) in HCV



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Sofosbuvir

Dasabuvir

- Daclatasvir: NS5A inhibitor
- Asunaprevir: NS3 protease inhibitor
  - Registered for genotype 1 including cirrhotics in Japan (June 2014)

SVR obtained….

- Sofosbuvir: Sovaldi®, 400 mg
- Simeprevir: Olysio®, 150 mg
- Sofosbuvir+Ledipasvir: Harvoni®, 400mg/90 mg
- Daclatasvir+ Asuneprevir: Daklinza® 60 mg +Sunvepra® 100 mg (2x1)
- (Ombitasvir 12,5 mg +Paritaprevir 75 mg + ritonavir 50 mg) Viekirax®, 1x2 + Dasabuvir: Exviera®, 250 mg, 2x1

Ribavirin
Is there still a place for it?

SVR
what is the new success standard?

- 60%?
- 70%?
- 80%?
- 90%?
- 100%?

- >90%
- If not?

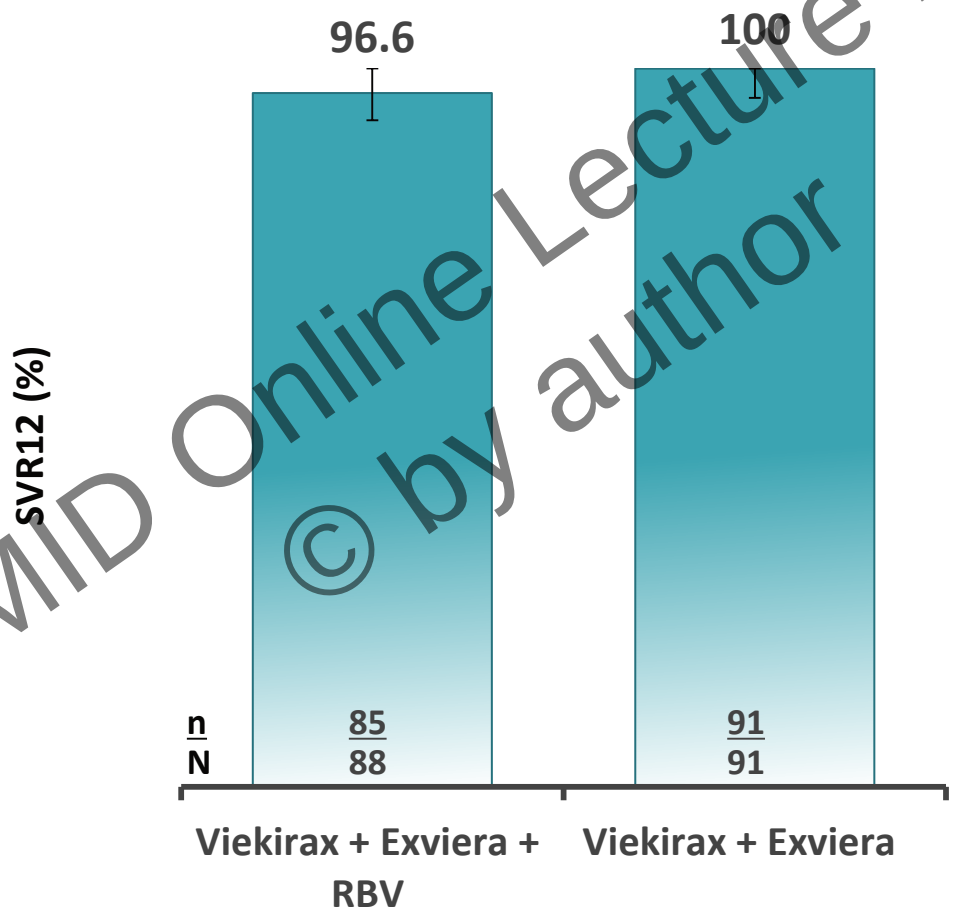
- >90%
- If not?
  - Add ribavirin
  - Prolong duration (12w---24w)
  - Both

Sofosbuvir (NI)+ Ledipasvir (NS5AI) RBV GT-1 (Phase III studies)

Study	Population	treatment	duration	SVR 12
ION-1	GT-1 treatment-naive (15.7% cirrhosis 136/865)	SOF/LDV	12 weeks	97.7% (209/214)
		SOF/LDV + RBV	12 weeks	97.2% (211/217)
		SOF/LDV	24 weeks	NA (N=217)
		SOF/LDV + RBV	24 weeks	NA (N= 217)
ION-2	GT-1 treatment-experienced (20% cirrhosis 88/440)	SOF/LDV	12 weeks	93.6% (102/109)
		SOF/LDV + RBV	12 weeks	96.4% (107/111)
		SOF/LDV	24 weeks	99.1 % (108/109)
		SOF/LDV + RBV	24 weeks	99.1% (110/111)
ION-3	GT-1 treatment-naive	SOF/LDV	8 weeks	94% (202/215)
		SOF/LDV + RBV	8 weeks	93.1% (201/216)
		SOF/LDV	12 weeks	95.4% (206/216)

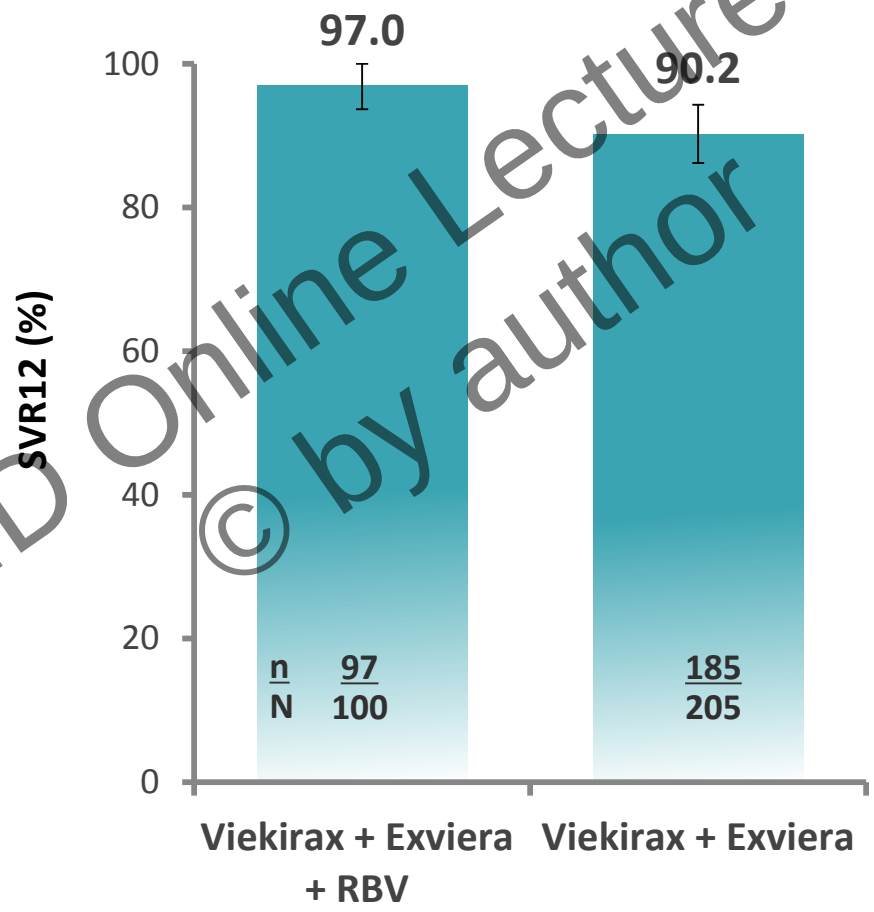
Gilead press release December 18th 2013

PEARL-II: GT1b, Non-Cirrhotic Patients



Andreone P, et al. Gastroenterology. 2014;147(2):359-365.e1.

PEARL-IV: GT1a, Naïve, Non-Cirrhotic Patients



Ferenci P, et al. N Engl J Med. 2014;370(21):1983-92.

TURQUOISE-II

The NEW ENGLAND JOURNAL of MEDICINE

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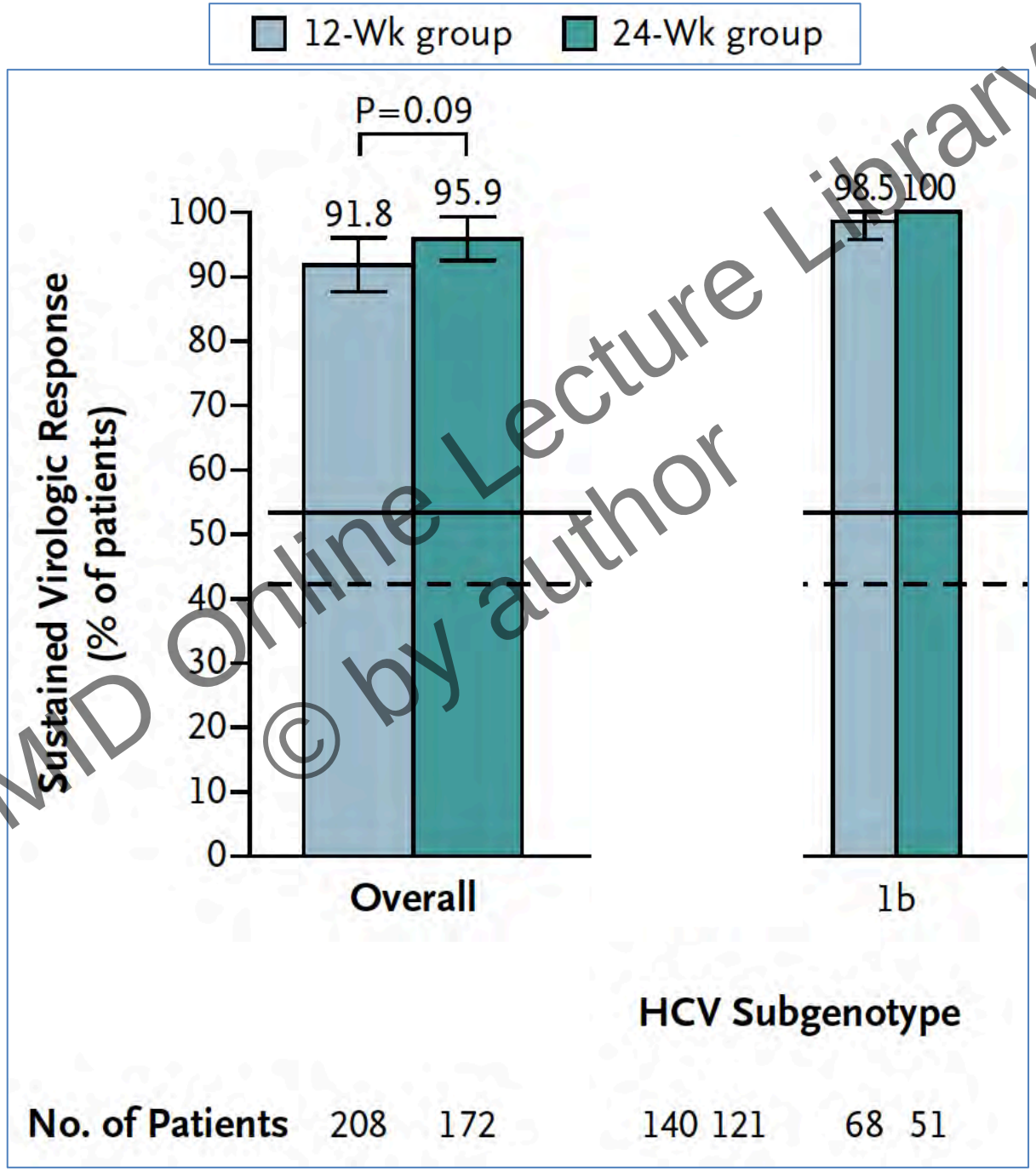
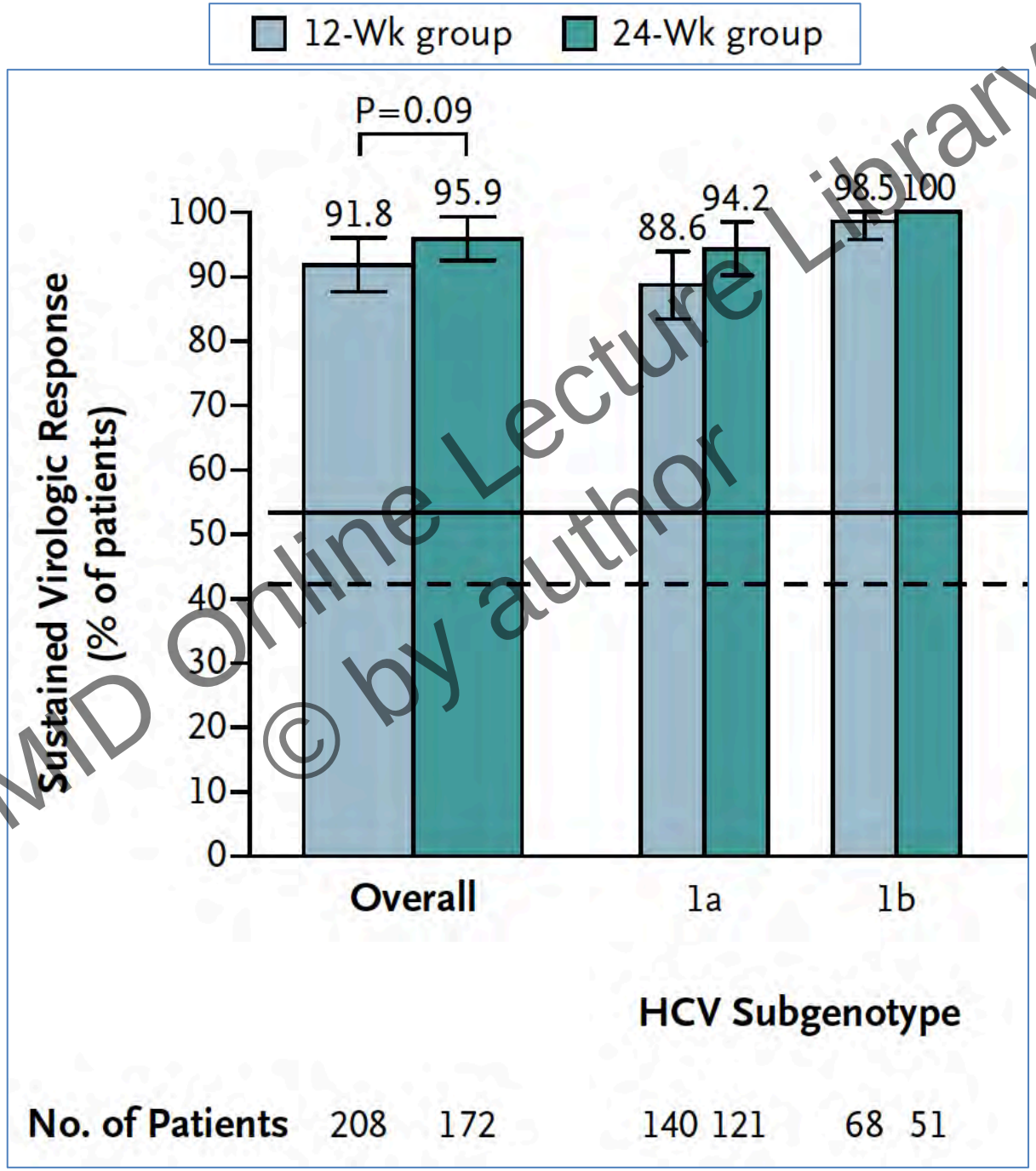
ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis

Fred Poordad, M.D., Christophe Hezode, M.D., Roger Trinh, M.D., M.P.H., Kris V. Kowdley, M.D., Stefan Zeuzem, M.D., Kosh Agarwal, M.D., Mitchell L. Shiffman, M.D., Heiner Wedemeyer, M.D., Thomas Berg, M.D., Eric M. Yoshida, M.D., Xavier Forns, M.D., Sandra S. Lovell, Ph.D., Barbara Da Silva-Tillmann, M.D., Christine A. Collins, Ph.D., Andrew L. Campbell, M.D., Thomas Podsadecki, M.D., and Barry Bernstein, M.D.



NEJM



NEJM

Gt1b
Non-cirrhotic

3D
12 w

BEST

WORST

Gt1b Non-cirrhotic	Gt1b cirrhotic	Gt1a Non-cirrhotic
3D 12 w	Add Riba to 3D (12 weeks)	Add Riba to 3D (12 weeks)

BEST

WORST

Gt1b Non-cirrhotic	Gt1b cirrhotic	Gt1a Non-cirrhotic	Gt1a cirrhotic
3D 12 w	Add Riba to 3D (12 weeks)	Add Riba to 3D (12 weeks)	Add Riba to 3D and prolong duration to 24 weeks

Multiple Treatments

- A 54-year-old male
- Anti-HCV positivity (screening)
- Genotype 1
- HCV-RNA: 3,340,000 IU/mL
- Obese, DM
- Liver Bx: Fibrosis 5/6 (Ishak's)
- In 2010, Peg-IFN+riba: Null responder

- 2013; Telaprevir and Boceprevir available
- Not re-imbursed for null-responders
- Permission for off-label use of boceprevir form Health Ministry
  - Lead-in with Peg-IFN+Riba
  - Added boceprevir at week 5

- Week 11: fatigue, anorexia, abdominal distention
  - US: mild ascites

Treatment?

- Treatment discontinued
- HCV-RNA
  - Week 8: negative
  - Week 11: negative
  - 3 months after discontinuation: 2,110,000 IU/mL

Comment

- This case does not represent a PI-failure
  - Premature discontinuation and relapse
- Cirrhotic and Peg-IFN+Riba-Nonresponder
  - SOF+LED 24 weeks or SOF+LED+Riba 12 weeks
  - 3D+Riba 12 weeks (Gt 1b) or 24 weeks (Gt1a)

PI Failures

- Peg-IFN+Riba+
  - Telaprevir, Boceprevir, Simeprevir
- SOF+LED or SOF+DCV (EASL)
- SOF+LED (AASLD)

Final Conclusion

- New SVR rate goal of HCV therapy is >90%
- New regimens provide
  - All oral
  - Short-duration
  - High SVR
- Challenges
  - Cirrhotics
  - Cost of drugs
  - Availability of drugs