State of the art of hepatitis C treatment: EASL 2016 recommendations

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ESCMID Postgraduate Education Course

Challenges in management of Viral Hepatitis

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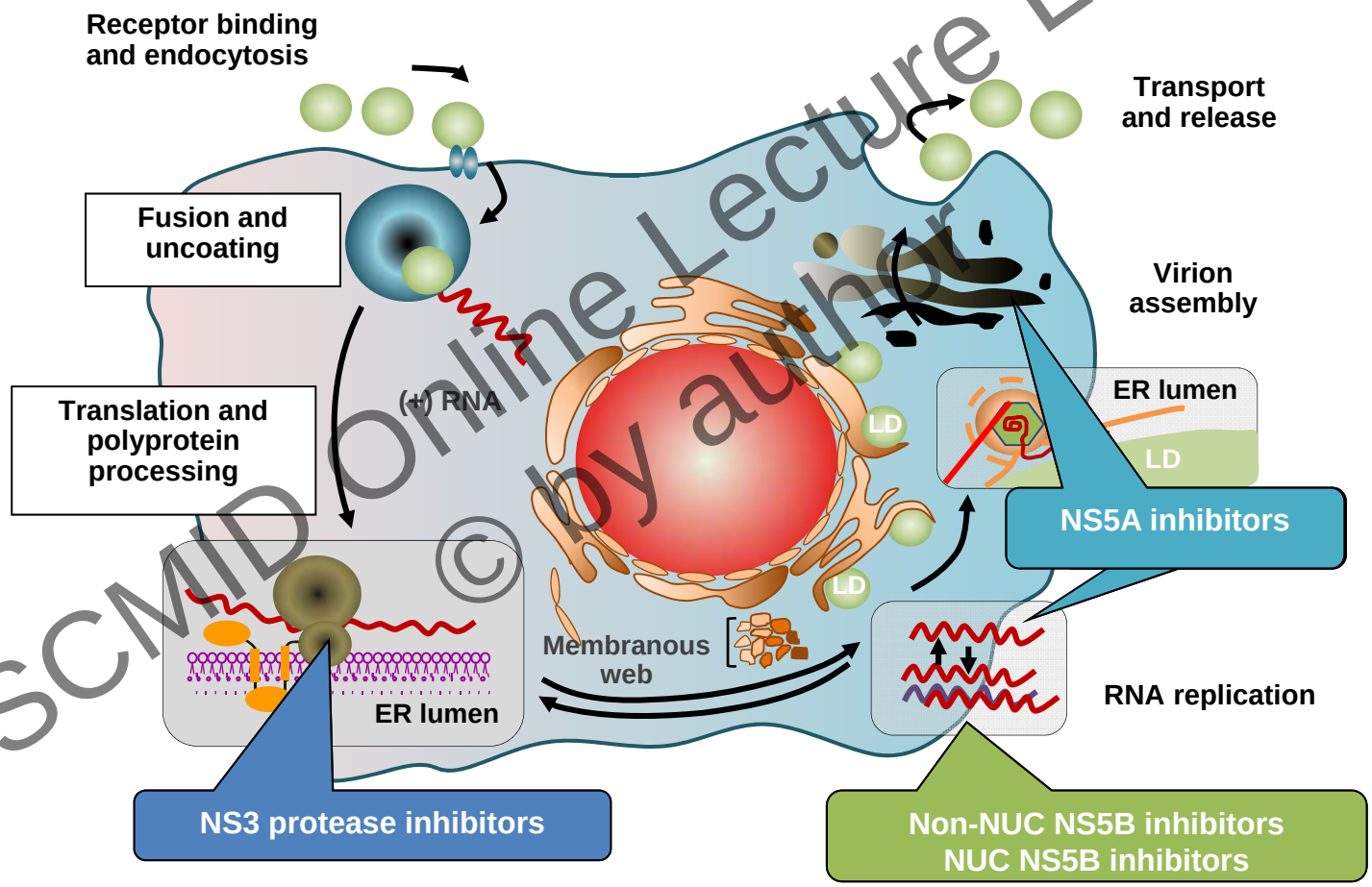
The HCV treatment landscape has changed dramatically in recent years

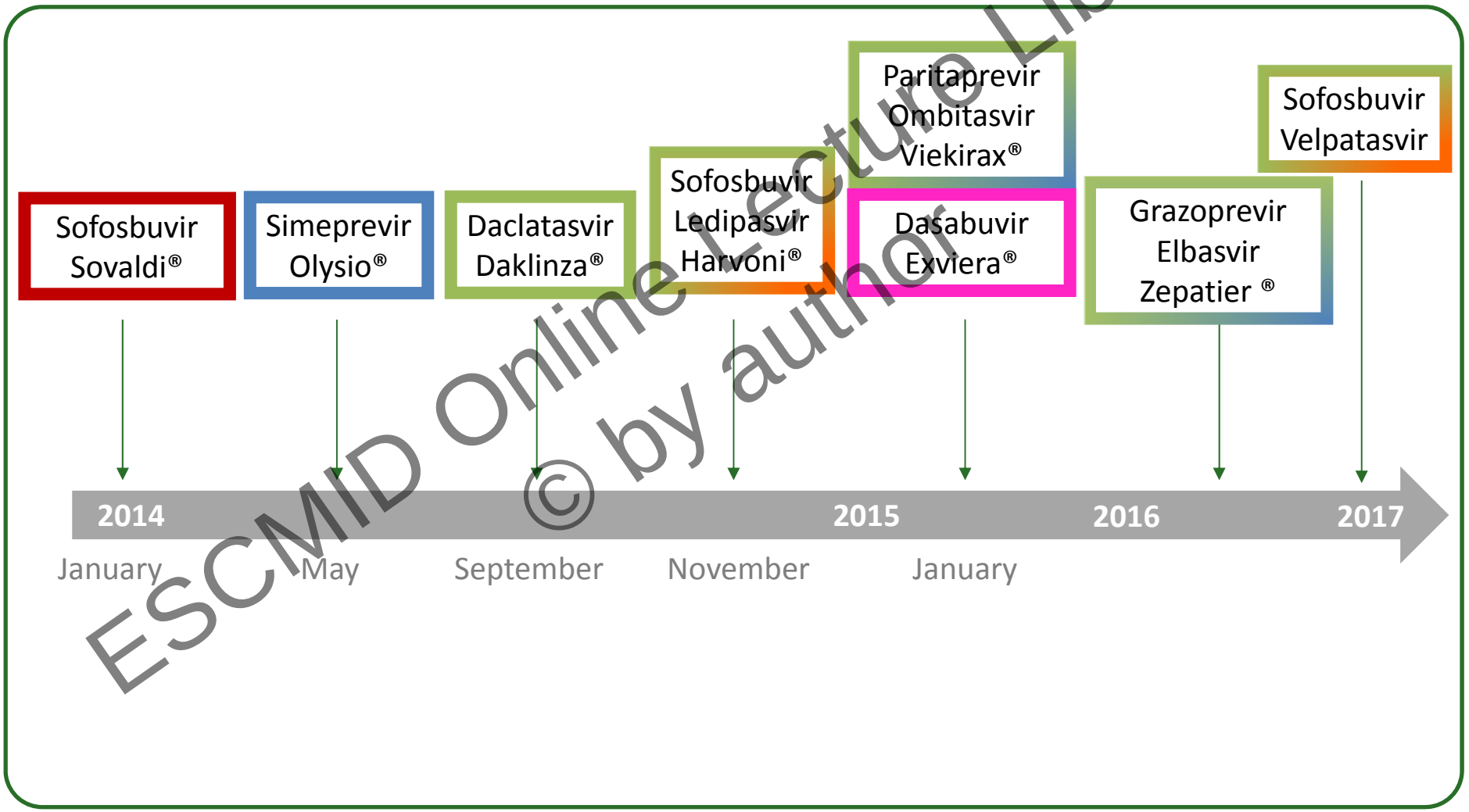
HCV life cycle and targets for direct-acting antiviral agents (DAAs)



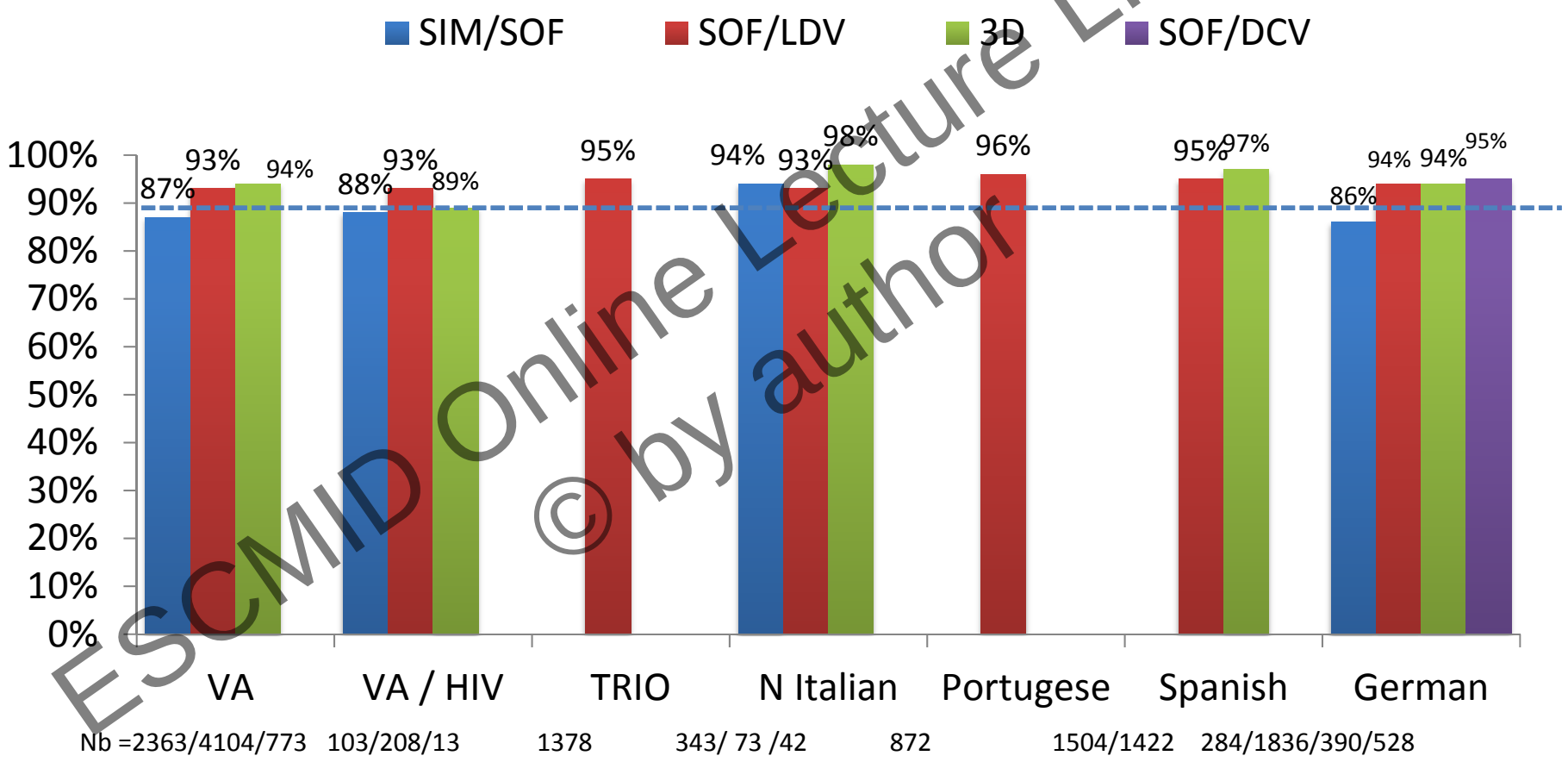
Adapted from Lindenbach BD, Rice CM. Nature 2005;436(Suppl):933–8

ER: endoplasmic reticulum; LD: luminal domain;
NS: non-structural protein; NUC: nucleotide analogue

Ten approved DAA drugs in Europe



Large real-world data confirm clinical trial results: more then GT-1 patients

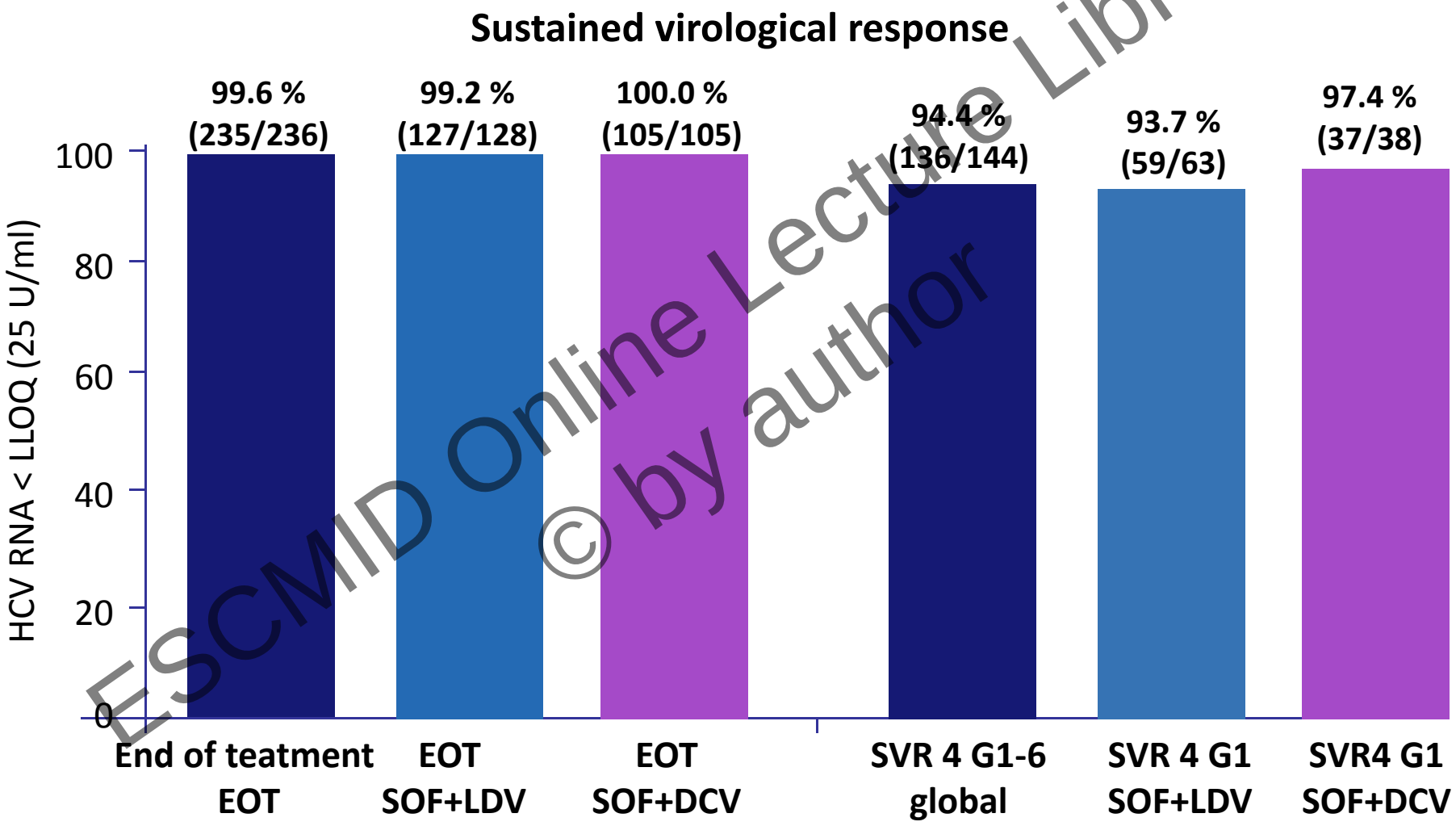


No impact of HIV HBV, diabetes and obesity on SVR

Hypo Alb <35g/l negative predictor of SVR

McCombs J et al: LBP-510,McGinnis J et al: LBP-514, Afdhal N et al: LBP-519, Aghemo A et al: LBP-500, Marinho T et al: LBP-523, Crespo, J et al: LBP-511, Calleja JL et al: LBP-512, Mauss. S et al: SAT-263

Generic drugs: a solution to HCV eradication worldwide



➔ **Very promising results although still to high price for some countries**

Freeman J, Australie, EASL 2016, Abs. LB03 actualisé

EASL 2016 Recommendations for the treatment of Hepatitis C

- Diagnosis
- Pretherapeutic assessement
- Who should be treated?
- How to treat ? *recommendations tailored by genotype*
- Special populations
- On-treatment and post-treatment monitoring
- Retreatment of non sutained virological responders
- Follow-up of untreated patients and virological failures
- Treatment of acute hepatitis

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Grading of recommendations EASL 2016 guidelines

		Grading
Quality of evidence	High	A
	Moderate	B
	Low	C
		Grading
Recommendation	Strong	1
	Weak	2

Adapted from GRADE system

Goals and end points of HCV therapy

- Goal : to cure HCV in order to prevent hepatic complications
- End point of therapy :
  - **HCV RNA undetectable at 12 or 24 weeks after the end of treatment by a sensitive test (LLD ≤ 15 IU/mL)**
  - Undetectable **HCV core antigen** : alternate end point.

Pre-therapeutic assessment

- **Other conditions of liver disease**
- **Fibrosis stage** *(by non invasive methods, reserve LB if uncertainty)*
- **Cardial and renal function**
- **HCV RNA quantification** (sensitive assay LLD ≤ 15 IU/mL)
- **HCV genotyping** (assay that discriminates 1a from 1b)
- Systematic resistance testing is not recommended

Contra-indications to therapy

- **Sofosbuvir**
  - Caution if renal clearance < 30 ml/min
  - Contra-indicated if amiodarone treatment and no possibility to switch to another treatment
- **NS3-4 protease inhibitor**
  - Contra-indicated in patients with decompensated cirrhosis (current or previous)

Who should be treated (1)?

- All HCV infected patients must be considered for therapy

- Treatment without delay for patients with:
  - **significant fibrosis or cirrhosis (F2, F3, F4)**
    - including decompensated cirrhosis
  - **Extra-hepatic manifestations with clincal symptoms**
    - symptomatic vasculitis with cryoglobulinemia, immune complex nephropathy, non hodgkin B cell lymphoma
  - **Recurrence after liver transplantation**
  - **Individuals at risk of transmitting HCV**
    - active PWID, MSM with high sexual behaviours, hemodialysis and incarcerated patients

Who should be treated (2)?

- Decompensated cirrhosis, Meld score ≥ 18-20 and indication for liver transplantation
  - => Transplantation 1st and treatment after

- Treatment non indicated if limited life expectancy due to non liver realted comorbidities

How to treat ?

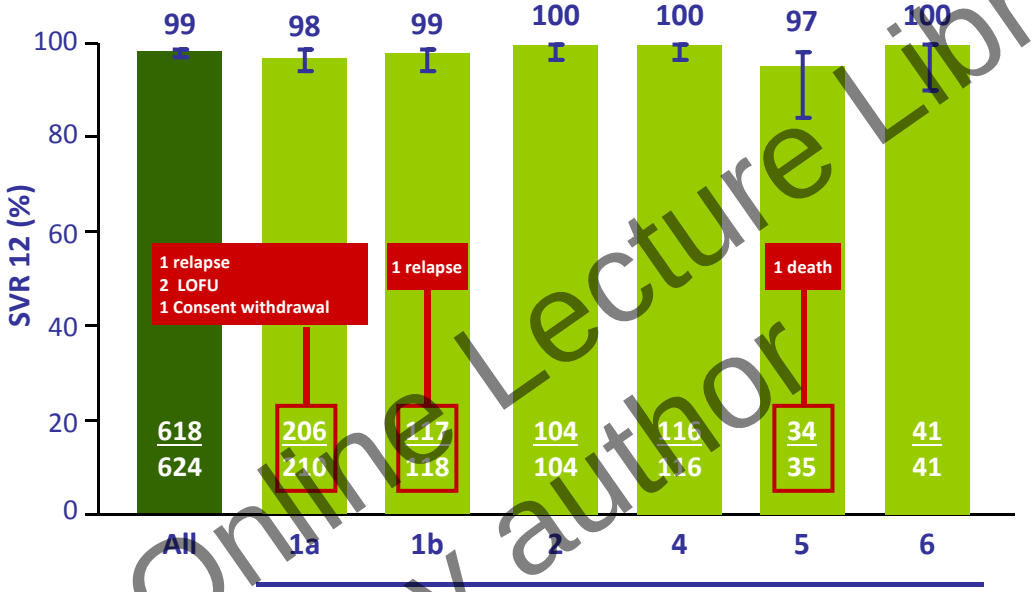
- **IFN-free regimens are the best options**
  - For all patients due to virological efficacy, easy use, tolerability
  - HIV Co-infected patients
    - same regimens as results are identical
    - changes or dose adjustements may be needed with ARV drugs.

- **Panel recognize that not all countries have full access to DAA but it is hoped that publication of these up-to-date guidelines will guide reimbursment, help negotiating and discounting of drug costs**

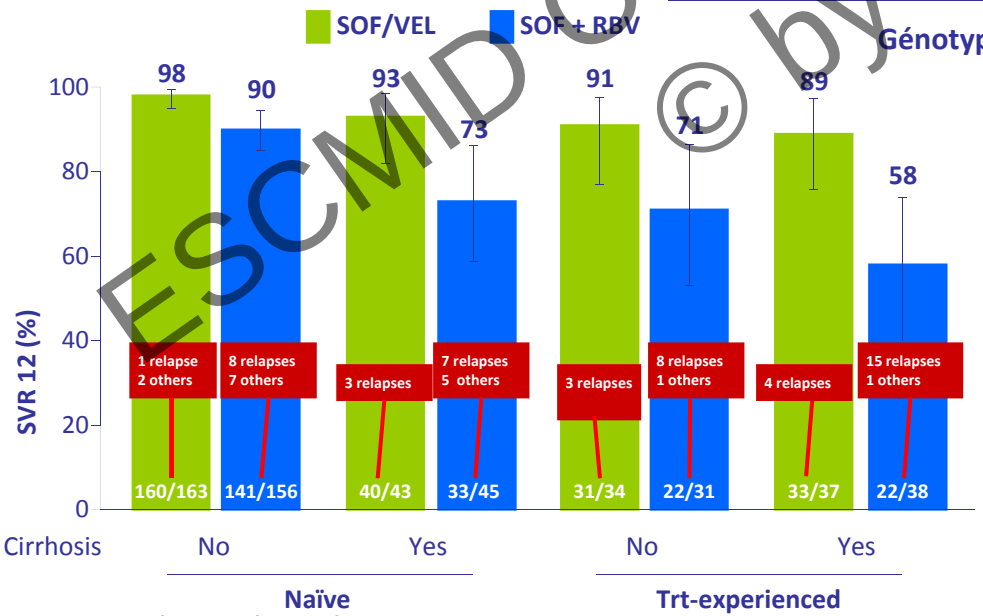
How to treat ? *General remarks*

- **Usual duration** : 12 weeks
- **Recommendations tailored by genotype**
  - 1b easier than 1a; G3 to most difficult to cure
- **Compensated cirrhosis :** same treatment and duration than for non cirrhotic patients
- **Ribavirin (1000-1200 mg in pts < and ≥ 75kg)**
  - **for experienced patients** (if velpatasvir, only for G3)
  - If NS5a mutation present
  - If contra-indication to RBV : extend to 24 weeks
- **Special recommendations for decompensated cirrhosis**

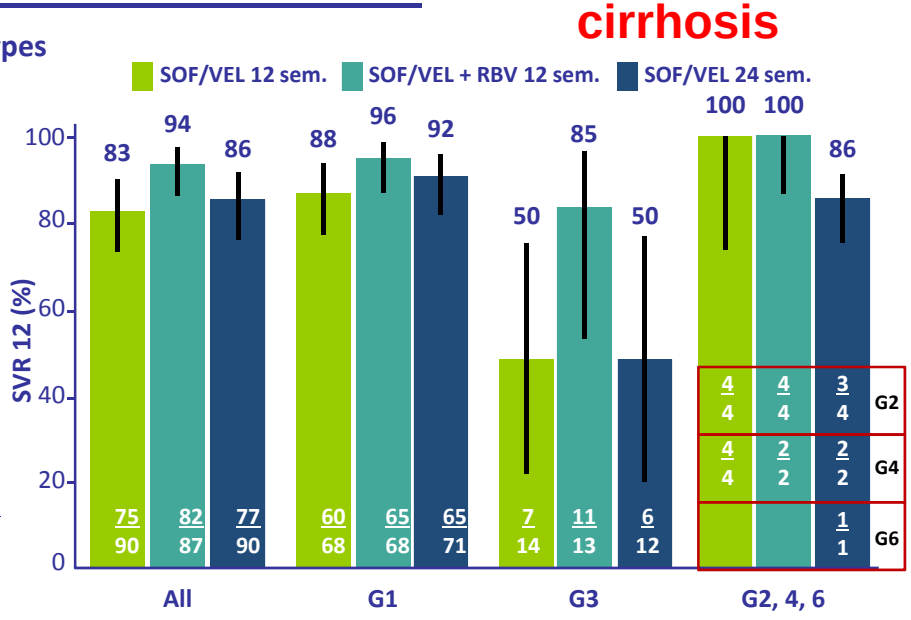
Sofosbuvir / velpatasvir



Genotype 3



Decompensated cirrhosis



Foster. GR et al. N Engl J Med 2015: 373: 2608-17

Feld. JJ et al. N Engl J Med 2015: 373: 2599-607

Curry.M et al. N Engl J Med 2015: 373: 2618-28

IFN-free valuable options for each genotype

These options are considered as equivalent for a given genotype

Combination	G1	G2	G3	G4	G5/6
Sofosbuvir+ribavirin	No	Subopt	Subopt	No	No
Sofosbuvir/ledipasvir +/- ribavirin	Yes	No	No	Yes	Yes
Sofosbuvir/velpatasvir +/- ribavirin	Yes	Yes	Yes	Yes	Yes
Ombitasvir/paritaprévir/R + dasabuvir +/- ribavirin	Yes	No	No	No	No
Ombitasvir/paritaprevir/RTV +/- ribavirin	No	No	No	Yes	No
Grazoprevir/elbasvir +/- ribavirin	Yes	No	No	Yes	No
Sofosbuvir+daclatasvir +/- ribavirin	Yes	Yes	Yes	Yes	Yes
Sofosbuvir+simeprevir +/- ribavirin	Subopt	No	No	Yes	No

Treatment for Genotype 1

Five options

Option 1 for genotype 1

- **Sofosbuvir 400mg/ Ledipasvir 90 mg**
  - Naive :
    - 12 weeks without RBV
  - Experienced
    - 1b: 12 weeks
    - 1a: 12 weeks with RBV or 24 weeks without RBV

8 weeks possible for
- G1 naive pts
- no cirrhosis
- HCV RNA < 6 M

Option 2 for genotype 1

- **Sofosbuvir 400mg/ Velpatasvir 100 mg**
  - Naive and experienced
    - 12 weeks without RBV

Option 3 for genotype 1

- **Ombitasvir /paritaprevir/ritonavir + dasabuvir**
  - 1b :
    - 12 weeks without RBV
    - 8 weeks possible for pts with no cirrhosis
  - 1a
    - 12 weeks with RBV

Doses : Ombitasvir 12,5 mg/paritaprevir 75 mg/ritonavir 50 mg + dasabuvir 250 mg

Option 4 : treatment for genotype 1

- **Grazoprevir 100 mg/elbasvir 50 mg**
  - 1b
    - 12 weeks without RBV
  - 1a
    - No resistance testing performed
      - HCV RNA < 800.000 IU/mL : 12 weeks without RBV
      - HCV RNA > 800.000 IU/mL : 16 weeks + RBV

Option 5 : treatment for genotype 1

- **Sofosbuvir 400mg/ Daclatasvir 60 mg**
  - Naive :
    - 12 weeks without RBV
  - Experienced
    - 1b: 12 weeks without RBV
    - 1a : 12 weeks with RBV, or 24 weeks if contraindication to RBV
  - Dose adaptation to 30 mg in HIV pts with atazanavir/r, cobisistat eviltegravir and to 90 mg if efavirenz

Treatment for genotype 2

Two following options

Treatment for genotype 2

- **Sofosbuvir 400mg/ Velpatasvir 100 mg**
  - Naive and experienced
    - 12 weeks without RBV
- **Sofosbuvir 400mg/ Daclatasvir 60 mg**
  - Naive or experienced
    - 12 weeks without RBV
- **Sofosbuvir/ribavirin or peg IFN/ribavirin**
  - suboptimal
  - Acceptable if other options not available

Treatment for genotype 3

Two following options

Option 2 for genotype 3

Two options

- **Sofosbuvir 400mg/ Daclatasvir 60 mg**
  - No cirrhosis
    - Naive
      - 12 weeks without RBV
    - Experienced
      - no RAVs testing : 12 weeks without RBV
      - RAVs testing if mutations : 12 weeks + RBV (ot 24 weeks if contra-indication to RBV)
  - Cirrhosis : 24 weeks + RBV

Option 1 for genotype 3

- **Sofosbuvir 400mg/ Velpatasvir 100 mg**
  - Naive without cirrhosis
    - 12 weeks without RBV
  - Experienced, naive with cirrhosis
    - 12 weeks with RBV
  - NS5a RAV testing available (technically challenging)
    - No Y93H : 12 weeks no RBV
    - Y93C : 12 weeks with RBV
  - Ribavirin contra –indicated : 24 weeks

In each country

Utility of give national recommendations by genotype function of available drugs

Génotype 1	Traitement	Durée (semaines)	Preuve
Génotype 1a cirrhose			
Naif	Sofosbuvir + Daclatasvir + ribavirine	12	A
	Sofosbuvir + Daclatasvir	24	A
	Sofosbuvir + Ledipasvir	12	A
	Dasabuvir + Ombitasvir + Paritaprevir/r + ribavirine	24	A
	Grazoprevir + Elbasvir + ribavirine	12	A
	Daclatasvir + Asunaprevir + Beclabuvir + ribavirine	12	A
	Sofosbuvir + Simeprevir + ribavirine	12	C
	Sofosbuvir + Simeprevir	24	C
Echec PEG - ribavirine	Sofosbuvir + Daclatasvir + ribavirine	12	A
	Sofosbuvir + Daclatasvir	24	A
	Sofosbuvir + Ledipasvir + ribavirine	12	A
	Sofosbuvir + Ledipasvir	24	A
	Dasabuvir + Ombitasvir + Paritaprevir/r + ribavirine	24	A
	Grazoprevir + Elbasvir	12	A
Génotype 1b cirrhose			
Naif	Sofosbuvir + Daclatasvir + ribavirine	12	A
	Sofosbuvir + Daclatasvir	24	A
	Sofosbuvir + Ledipasvir	12	A
	Dasabuvir + Ombitasvir + Paritaprevir/r + ribavirine	12	A
	Grazoprevir + Elbasvir + ribavirine	12	A
	Daclatasvir + Asunaprevir + Beclabuvir	12	A
	Sofosbuvir + Simeprevir + ribavirine	12	C
	Sofosbuvir + Simeprevir	24	C
Echec PEG - ribavirine	Sofosbuvir + Daclatasvir + ribavirine	12	A
	Sofosbuvir + Daclatasvir	24	A
	Sofosbuvir + Ledipasvir + ribavirine	12	A
	Sofosbuvir + Ledipasvir	12	A
	Dasabuvir + Ombitasvir + Paritaprevir/r + ribavirine	12	A
	Grazoprevir + Elbasvir	12	A
	Daclatasvir + Asunaprevir + Beclabuvir + ribavirine	12	B
Génotype 1a et 1b cirrhose			
Echec Telaprevir ou Boceprevir	Sofosbuvir + Ledipasvir + ribavirine	12	A
	Sofosbuvir + Ledipasvir	24	A
	Sofosbuvir + Dclatasvir + ribavirine	12	A
	Sofosbuvir + Daclatasvir	24	A
	Grazoprevir + Elbasvir + ribavirine	12	B
	Sofosbuvir + GS-5816	12	A
Autres échecs	Avis d'expert recommandé		
Cirrhose décompensée			
	xxxxxxxxx		
Génotype 1a non cirrhotique			
Naif	Sofosbuvir + Daclatasvir	12	A

Special groups

Decompensated cirrhosis (on waiting list)

- **Contra-indication to IFN-based therapies**
- **Meld score < 18-20 : DAA before transplantation**
  - SOF/LDV, SOF/VPV, SOF/DVC
  - If RBV needed : 600 mg; if RBV contra-indicated extend duration to 24 weeks
- **Meld score ≥ 18-20 : transplantation first**
  - Except if waiting list time > 6 months
- **HCC awaiting liver transplantation : DAA before transplantation**

Meld score calcul takes into account bilirubin, INR and creatinin. It predicts survival at 3 month : Score 10-19 : 6%; score > 19: 19,6%

Decompensated cirrhosis (not on waiting list)

- Child B and Child C up to 12, no concomitant comorbidities limiting survival = > treatment with DAA urgently
- HCC and not a the waiting list : lack of data and conflicting results

Meld score calcul takes into account bilirubin, INR and creatinin. It predicts survival at 3 month : Score 10-19 : 6%; score > 19: 19,6%

HCV/HBV coinfection

- HBV DNA often low or undectectable
- Potential risk of HBV reactivation after HCV cure
- If chronic (HBsAg) or occult HBV (anti HBc) => concurrent HBV therapy indicated

Extra hepatic manifestations of HCV due to immune complexes

- **DAA efficacy proven**
  - on clinical signs of mixed cryoglobulinemia
  - On early low grade lymphoma : reports of DAA efficacy
  - Renal disease (?) : rituximab to be discussed

Other risk groups

- Renal impairement and hemodialysis
- Solid organ transplants
- Haemoglobinopathies
- Bleedind disorders

Treatment monitoring

Monitoring of efficacy

By real-time PCR (LLD < 15 UI/mL)

- **Usual**
  - Baseline
  - Week 2 or 4 (optional to monitor adherence)
  - End of treatment
  - 12- 24 weeks post treatment (SVR)

- **Simplified**
  - Baseline
  - 12- 24 weeks post treatment (SVR)

Monitoring of biological safety

- **ALT levels**
  - W 2, 4 and monthly
  - If increase, test Hbs Ag or HBV DNA
- **Renal function**
  - regularly on sofosbuvir
  - Not recommended if < 30 ml/min
- **Indirect bilirubin**
  - if simprevir, paritaprevir

Safety : main AE and rate pts discontinuing for AE

	Main reported AE	% stopping for AE
Sofosbuvir/ledipasvir	Fatigue, headache Few cases pulmonary arterial hypertension : link not established	< 1%
Sofosbuvir/velpatasvir	Faitgue, headache	<1%
Paritaprevir/r/ombitasvir/ dasabuvir	Pruritus, fatigue, nausea, insomia Transient ALT increases ALT* ,and indirect bilirubin**	1-2%
Grazoprevir/elbasvir	Fatigue, headache, nausea, transient ALT increases ALT*	2.4%
Daclatasvir	Fatigue, headache, nausea,	
Siméprévir	Fatigue, nausea, insomia, pruritus, rash, photosentitivity (sun protection necessary),	
Ribavirin	Anemia, teratogenic effect	

* Mainly if oestreogen comedication **Inhibition of bilirubin transporter with paritaprevir

Monitoring of drug-drug interactions

- **Review of all the drugs taken by the patient**
  - Including over-the-counter and recreational drugs

- **When possible, an interacting comedication should be stopped or switched for the duration of HCV treatment (statin)**

Dose reduction

- **Hemoglobin**
  - < 10 g/dl : decrease RBV by 200 mg decrements
  - < 8 g/dl : stop RBV
- **Stop therapy in case of**
  - ALAT flare > 10 N
  - Bacterial infection
  - AE of unclear origin

Adherence

- **Suboptimal adherence is associated with virological breakthrough**

  ⇒Ressources must be devoted for counselling on the importance of adherence,

  - before and during treatment
  - Especially to patients with poor conditions and migrants, drug users , alcohoolic

Post treatment follow-up

- Non cirrhotic and not at risk of reinfection
  - HCV RNA and ALT 48 weeks post treatment
  - then surveillance can be stopped

- F3 and F4 cirrhotics and on going at risk behaviors (PWID, MSM) => next talk

Retreatment of non sustained virological responders after DAA combination

DAA-class, RBV, duration

p1

- **Multidiciplinary assessment**
- **Re-treat with sofosbuvir as a DAA with a very high barrier to resistance**
- **Switch of DAA class if possible (G1, 4)**

  Protease-inhibitor ⟹ NS5A-inhibitor

  NS5A-inhibitor ⟹ Protease-inhibitor

- **Add Ribavirin if Metavir score F ≥ 2**
- **Extend treatment duration to 24 weeks and add ribavirin if fibrosis score ≥F3**

p1

ajouter une ou deux dias sur
le vaccin
l'immunogénicité
la protection
l'innocuité
pc; 02.03.2014

Retreatment of non sustained virological responders

- **No urgent need of HCV treatment => wait** until more data, or alternative therapeutic options available.

- Utility of HCV resistance testing prior to retreatment = unknown!

- If testing performed, retreatment guided by probabilities of response according to the resistance team.

Retreatment of non sustained virological responders

Failure after	Treatment with	Duration / RBV
telaprevir, boceprevir or simeprevir	SOF + NS5a inhibitor	12 weeks
SOF alone or RBV/Peg IFN	easl recos	24 weeks in F0-F2 patients with HCVRNA >800,000 IU/ml
G 1 or 4 after SOF SIM	SOF + NS5a	
G 1 or 4 after SOF/NS5a inhibitor	SOF + paritaprevir/r, ombitasvir/ dasabuvir (G1) or SOF+ grazoprevir and elbasvir (G 1 and 4) or SOF+ simeprevir+ daclatasvir (G1 or 4)	12 weeks (G 1b or 4 and METAVIR F0 to F2) 24 weeks (all G 1a; G1b and 4 patients with METAVIR F3 or compensated cirrhosis) With RBV
G 2, 3, 5 or 6 after SOF/ NS5A inhibitor	SOF+ VPV	24 weeks with RBV

Treatment of acute hepatitis C

- **HCV monoinfection**
  - sofosbuvir/ledipasvir (G1, 4, 5, 6) or
  - sofosbuvir/velpatasvir (all genotypes), or
  - sofosbuvir/daclatasvir (all genotypes)
  - for **8 weeks without RBV.**

- **HIV coinfection or baseline HCV RNA >1 million IU/ml (6.0 log IU/ml)**
  - same combination regimens
  - **12 weeks**

- SVR assessed at 12 **and 24 weeks post-treatment**, as late relapses have been reported.

Conclusion

- IFN-free regimens are the best options for all patients
- Type of regimen and duration are mainly tailored HCV genotypes
- For HIV co-infected : same regimens
- Panel recognize that not all countries have full access to DAA but it is hoped that publication of these up-to-date guidelines will guide reimbursment, help negotiating and discounting of drug costs
- Every country will have to adapt these recommandations in its national guidelines and elimination plan.

Thanks to the panel

- Jean-Michel Pawlotsky
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- Geoffrey Dusheiko
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- Massimo Puoti
- Christoph Sarrazin

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www.easl.eu

www.hcvguidelines.org